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REVIEW ARTICLE

Japanese Guideline for Adult Asthma 2014

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ABSTRACT

Adult bronchial asthma (hereinafter, asthma) is characterized by chronic airway inflammation, reversible airway narrowing, and airway hyperresponsiveness. Long-standing asthma induces airway remodeling to cause intractable asthma. The number of patients with asthma has increased, and that of patients who die from asthma has decreased (1.5 per 100,000 patients in 2012). The aim of asthma treatment is to enable patients with asthma to lead a normal life without any symptoms. A good relationship between physicians and patients is indispensable for appropriate treatment. Long-term management with antiasthmatic agents and elimination of the causes and risk factors of asthma are fundamental to its treatment. Four steps in pharmacotherapy differentiate between mild and intensive treatments; each step includes an appropriate daily dose of an inhaled corticosteroid, varying from low to high. Long-acting β_2-agonists, leukotriene receptor antagonists, and sustained-release theophylline are recommended as concomitant drugs, while anti-immunoglobulin E antibody therapy has been recently developed for the most severe and persistent asthma involving allergic reactions. Inhaled β_2-agonists, aminophylline, corticosteroids, adrenaline, oxygen therapy, and others are used as needed in acute exacerbations by choosing treatment steps for asthma exacerbations depending on the severity of attacks. Allergic rhinitis, chronic obstructive pulmonary disease, aspirin-induced asthma, pregnancy, asthma in athletes, and cough-variant asthma are also important issues that need to be considered.

KEY WORDS

diagnosis of adult asthma, epidemiology of asthma, long-term management, management of acute exacerbations, specific considerations

1. Aim of the Management, Definition, Type, Diagnosis, and Severity of Asthma

1.1. Definition and Pathophysiology of Asthma

Adult bronchial asthma (hereinafter, asthma) is characterized by repetitive cough, wheezing, dyspnea, reversible airflow limitation, and airway hyperresponsiveness. Asthma symptoms tend to be more severe in more hyperresponsive airways, but airway hyperresponsiveness is not always associated with asthma symptoms. Pathological findings in asthma include chronic airway inflammation accompanied by the in-

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Table 1 Aims of asthma treatment

1. To lead a normal and healthy life, and maintain normal growth.
2. To maintain normal respiratory function:
Peak expiratory flow (PEF) variation, <20% of the predicted value;
PEF, ≥80% of the predicted value.
3. To ensure sufficient night sleep without cough or dyspnea at night or in the early morning.
4. To prevent asthma attacks.
5. To prevent death from asthma.
6. To prevent adverse effects caused by therapeutic agents.
7. To prevent the development of irreversible airway remodeling.

Table 2 Differential diagnosis for asthma

1. Upper respiratory tract diseases: laryngitis, epiglottitis, vocal cord dysfunction
2. Proximal respiratory tract diseases: endotracheal tumor, foreign body aspiration, tracheomalacia, endobronchial tuberculosis, sarcoidosis
3. Diseases of the bronchus and alveolar regions: chronic obstructive pulmonary disease, diffuse panbronchiolitis, pulmonary fibrosis, hypersensitivity pneumonitis
4. Cardiovascular diseases: congestive heart failure, pulmonary thromboembolism
5. Cough induced by medicines, such as angiotensin-converting enzyme inhibitors
6. Other causes: spontaneous pneumothorax, vagotonic effects, hyperventilation syndrome, and psychogenic cough
7. Allergic respiratory diseases: allergic bronchopulmonary mycosis, eosinophilic granulomatosis with polyangiitis (EGPA) (allergic granulomatous angiitis, Churg-Strauss syndrome), eosinophilic pneumonia

Table 3 Diagnosis of adult asthma: key features

1. Recurrence of paroxysmal dyspnea, wheezing, and cough (particularly at night and in the early morning)
2. Reversible airflow limitation: improvement with time or treatment. Diurnal variation in the peak expiratory flow rate, ≥20%. Forced expiratory volume in one second increased by ≥12% and ≥200 mL of the absolute volume by β_2-agonist inhalation
3. Airway hyperresponsiveness: increased airway contractility to acetylcholine, histamine, or methacholine
4. Atopy: IgE antibodies against environmental allergens
5. Airway inflammation: increased levels of eosinophils and ECP in sputum and peripheral blood, Creola bodies; increased fraction of exhaled nitric oxide
6. Differential diagnosis: exclude other cardiopulmonary diseases

ECP, eosinophil cationic protein.

filtration of proinflammatory cells such as eosinophils, lymphocytes, mast cells, and others, and by the detachment of the airway epithelial cells.[1,2] While many patients have immunoglobulin E (IgE) antibodies against environmental allergens, airway inflammation and lymphocyte activation are noted even in patients without allergen-specific IgE antibodies. The etiology of asthma is multifactorial, and its clinical picture varies greatly among patients; thus, different clinical pictures of asthma have attracted attention. Some patients show airway inflammation with predominating neutrophils. Patients with long-standing asthma show airway remodeling, involving subepithelial fibrosis under the basement membrane, smooth muscle hypertrophy, and submucosal gland hyperplasia, which results in intractable asthma with irreversible airflow limitation and persistent airway hyperresponsiveness.[3]

1.2. Aim of the Management and Treatment of Asthma (Table 1)

The aim of the management and treatment of asthma is to alleviate airway hyperresponsiveness and airflow limitation by eliminating the inducers of airway inflammation and airflow limitation, by using pharmacotherapy to suppress inflammation, and by dilating the constricted airway. Respiratory function is normalized as much as possible to improve the patients' quality of life (QOL) and enable them to lead a normal and healthy life.

1.3. Diagnosis of Adult Asthma

Diagnosing mild asthma without either wheezing or dyspnea is sometimes difficult. Generally, clinical diagnosis of asthma is based on the following factors: (i) repetitive symptoms such as paroxysmal dyspnea,

wheezing, chest tightness, and cough; (ii) reversible airflow limitation; and (iii) exclusion of other cardiopulmonary diseases (Table 2). The diagnostic criteria for asthma have not been established. Instead, the signs suggestive of asthma are presented in Table 3.

1.3.1. Recurrence of paroxysmal dyspnea, wheezing, chest tightness, and cough

Asthma is characterized by repeated exacerbations that occur amid symptom-free intervals and develop even at rest. Patients with asthma may experience dyspnea (choking) during exercise and laborious work. Asthma with such symptoms, occurring over the past 12 months, is called current asthma. The diagnosis of asthma is supported by a history of (i) the development and persistence of dyspnea; (ii) emergency room visits and hospitalization owing to paroxysmal dyspnea, (iii) improvement of symptoms when using an antiasthmatic drug, and (iv) dyspnea caused by exposure to certain triggering factors.

1.3.2. Reversible airflow limitation[4]

Wheezing and dyspnea during attacks are caused by reversible airway narrowing, which develops in the airways diffusely and ranges from mild to severe. In its mild form, it can be detected only by respiratory function tests, while its severe form could even induce near-fatal exacerbations. The peak expiratory flow (PEF) and forced expiratory volume in one second (FEV_1) differ markedly between exacerbations and controlled periods. Asthma-specific alterations in PEF and FEV_1 have not been established, but a diurnal variation in PEF of 20% and higher suggests asthma. Reversible airflow limitation is regarded as significant when FEV_1 is increased by 12% or more and 200 mL or more of the absolute volume after β_2-agonist inhalation. If the increase is below that level after β_2-agonist inhalation, reversibility may be detected after oral corticosteroid administration for 2 to 3 weeks. In addition, even if no significant difference is noted in respiratory function tests before and after β_2-agonist inhalation, asthma is still suspected when there is a significant difference (≥20%) between the PEF rates before using a bronchodilator in the early morning and those after inhaling a β_2-agonist between 12:00 pm and 14:00 pm.

1.3.3. Airway hyperresponsiveness[5,6]

The airway is contracted by stimuli to which healthy individuals show no response. A standard quantitation method of the Japanese Society of Allergology to monitor the changes in FEV_1 or a method with an Astograph, which measures respiratory system impedance, can be used. In the former method, a patient inhales a bronchoconstrictor (e.g., acetylcholine, methacholine, or histamine) for 2 min each before the assessment of FEV_1. PC_{20} (i.e., a concentration to reduce FEV_1 by 20%) and PD_{20} (i.e., a cumulative dose during that time) represent airway responsiveness. In the latter method, a patient automatically inhales serially diluted methacholine. Airway hyperresponsiveness is assessed as Dmin, the concentration of methacholine at which airway resistance starts to increase. Both methods are load tests that induce airway narrowing; thus, patients with decreased respiratory function should be treated with caution. A desirable baseline percentage of FEV_1 against a predicted value ($\%FEV_1$) is 70% or higher.

1.3.4. Atopic state

Specific IgE antibodies against various environmental allergens indicate an atopic state.

1.3.5. Airway inflammation

Increased percentages of eosinophils, high eosinophil cationic protein values, and creola bodies consisting of exfoliated airway epithelial cells, detected by sputum examination, indicate allergic airway inflammation.[7] An increased fraction of exhaled nitric oxide (FeNO) also suggests eosinophilic airway inflammation, and is often observed in untreated asthma.[8,9] An increased eosinophil count in the peripheral blood and elevated serum levels of eosinophil cationic protein also suggest airway inflammation.

Of the above signs, respiratory symptoms (1.3.1.) and reversible airflow limitation (1.3.2.), as well as asthma symptoms not caused by other cardiopulmonary diseases (1.3.6.) are diagnostically important. If the respiratory function is normal, the presence of airway hyperresponsiveness (1.3.3.) and allergic airway inflammation (1.3.5.) support the diagnosis of asthma.

1.3.6. Differential diagnosis

A comprehensive diagnosis should be made if boundary regions of asthma-like symptoms, caused by other cardiopulmonary diseases, or a state coexisting with asthma are considered (Table 2).

1.4. Classification of the Severity of Asthma and Asthma Exacerbation

Assessment of the severity of asthma and its exacerbation is important for the management of asthma and a stepwise approach to pharmacotherapy (Table 4). The severity of untreated asthma is classified as mild intermittent, mild persistent, moderate persistent, or severe persistent (Table 4). These categories correspond to the recommendation of treatment steps from 1 to 4, respectively (Table 5). In patients receiving treatment, the symptoms and the present treatment step determine the actual severity (Table 6). The classification of exacerbations according to severity is presented in Table 7.

1.5. Intractable Asthma

Intractable asthma is one of the most severe and per-

Table 4 Classification of asthma severity based on clinical findings before treatment (adults)

Severity†		Mild intermittent	Mild persistent	Moderate persistent	Severe persistent
Features of asthma symptoms	Frequency	Less than once a week	Once or more a week, not every day	Every day	Every day
	Intensity	Mild and brief	Disturbs daily life or sleep once or more a month	Disturbs daily life or sleep once or more a week	Restricts daily life
				Short-acting inhaled β_2 agonist is needed almost every day	Frequently exacerbated even under treatment
	Symptoms at night	Less than twice a month	Twice or more a month	Once or more a week	Frequently
PEF FEV_1‡	$\%FEV_1$, %PEF	≥80%	≥80%	≥60%, <80%	<60%
	Diurnal variation of PEF	<20%	20-30%	>30%	>30%

† Determine the severity based on the presence of any one of the features.

‡ In patients with severe or long-standing symptoms, severity may be underestimated when determined based on symptoms. Respiratory function indicates the objective severity of airway obstruction. Its variation is associated with airway hyperresponsiveness. $\%FEV_1$, (FEV_1 measured value/FEV_1 predicted value) × 100; %PEF, (PEF measured value/PEF predicted value or the best value) × 100.

sistent types of asthma, with daily presence of symptoms, even if step 4 treatment is administered, involving inhaled corticosteroids (ICSs), long-acting β_2-agonists (LABAs), leukotriene receptor antagonists (LTRAs), and theophylline (Table 5, 6). Additional potential underlying diseases such as aspirin-exacerbated respiratory disease (AERD; also known as aspirin-intolerant asthma and aspirin-induced asthma, AIA), eosinophilic granulomatosis with polyangiitis (EGPA; also known as Churg-Strauss syndrome, CSS) and other systemic vasculitis syndromes, and allergic bronchopulmonary mycosis (ABPM), represented by allergic bronchopulmonary aspergillosis (ABPA), should be considered in patients requiring continuous oral corticosteroid administration.

2. Epidemiology of Asthma

2.1. Changes in Asthma Prevalence over Time

Asthma prevalence has been rapidly increasing in recent years. An International Study of Asthma and Allergies in Childhood (ISAAC) survey was conducted across Japan to examine the prevalence of asthma at specific time points. The mean prevalence in Japan was estimated to have increased from about 1% to 10% or higher in children and to about 6% to 10% in adults since the 1960s. In addition, according to a survey conducted over several years, in which the same physicians used the same protocol in subjects with the same background (Table 8),[10,11] a 1.5- to 2-fold increase in the prevalence of asthma was reported every 10 years. In a survey of adult asthma among the citizens of Fujieda City in Shizuoka Prefecture conducted in 1985, 1999, and 2006, the prevalence of adult asthma has been increasing, while the latest studies of children in Western Japan have shown the decrease in the prevalence of asthma (Table 8).

2.2. Regional Differences in Asthma Prevalence

The ISAAC Steering Committee reported notable regional differences in the prevalence of asthma: 3.5% in Indonesia, 34.8% in Costa Rica in 6- to 7-year-old subjects, 3.0% in Albania, and 32.3% in the Isle of Man in 13- to 14-year-old subjects. The prevalence in Japan was slightly lower than that in Europe and the USA (e.g., Fukuoka City, 13%). A comparison of the European Community Respiratory Health Survey and Japanese studies showed that the prevalence of asthma in Japan was lower (8.1%), although the surveys were conducted in different years (Table 9).[12]

2.3. Male-to-Female Ratio

The prevalence of asthma is more common in men at an early age worldwide; however, after puberty, the prevalence is more common in women (Fig. 1). At the onset of asthma, the male-to-female ratios in Japan were 1.4 during infancy (0-5 years of age), 1.0 during childhood (6-17 years of age), and 0.8 in adulthood (18 years of age and older).

2.4. Number of Patients

According to the 2011 Statistical Information of the Japanese Ministry of Health, Labour, and Welfare, the number of patients with asthma, who had contin-

Table 5 Treatment steps for asthma

		Treatment step 1	Treatment step 2	Treatment step 3	Treatment step 4
Long-term management agents	Basic treatment	Inhaled corticosteroid (low dose)	Inhaled corticosteroid (low to medium doses)	Inhaled corticosteroid (medium to high doses)	Inhaled corticosteroid (high dose)
		If the above agent cannot be used, use one of the following agents. ・LTRA ・Theophylline sustained-release preparation (unnecessary for rare symptoms)	If the above agent is ineffective, concomitantly use one of the following agents. ・LABA (a compounding agent can be used) ・LTRA ・Theophylline sustained-release preparation	Concomitantly use one or more of the agents below. ・LABA (a compounding agent can be used) ・LTRA ・Theophylline sustained-release preparation	Concomitantly use multiple agents of those below. ・LABA (a compounding agent can be used) ・LTRA ・Theophylline sustained-release preparation If poorly controlled with all of the above agents, add either or both of the agents below. ・Anti-IgE antibody ‡ ・Oral corticosteroid §
	Additional treatment	Antiallergics other than LTRA †	Antiallergics other than LTRA †	Antiallergics other than LTRA †	Antiallergics other than LTRA †
Exacerbation treatment¶		Inhaled SABA	Inhaled SABA	Inhaled SABA	Inhaled SABA

LTRA, leukotriene receptor antagonists; LABA, long-acting β_2 agonist; SABA, short-acting β_2 agonist.

† Antiallergics refer to mediator antireleasers, histamine H_1 antagonists, thromboxane A_2 inhibitors, and Th2 cytokine inhibitors.

‡ Anti-IgE antibody is indicated for patients who are positive for perennial inhaled allergen with serum total IgE value of 30-700 IU/mL.

§ Oral corticosteroids are intermittent administration for a short period. Keep the minimum maintenance dose if a patient cannot be controlled by enhanced treatment with other agents and short intermittent administration.

¶ Management against mild exacerbations is shown. For other exacerbations, refer to Table 22, 23.

In steps 2 and 3 of the treatment, in patients treated with a combination of budesonide/formoterol as a controller, if used as a rescue, the agent should be used within the maximum number of uses for each time and day. The maximum number of uses is generally up to 8 inhalations/day; however, temporarily, it can be used up to 12 inhalations/day (for 3 days: budesonide, 1920 μg/day; formoterol 54 μg/day). When more than 8 inhalations/day of budesonide/formoterol are needed, a physician should be consulted.

ued to visit the hospital until the survey in October 2011, was 1,045,000 (521,000 men and 523,000 women). The number was calculated as the number of hospitalized patients + new outpatients + second visit outpatients × average visit interval × survey coefficient. Medical treatment rates in the hospital and outpatient settings are in Table 10. In a large-scale telephone survey, conducted in 2011 (Asthma Insight and Reality in Japan, AIRJ2011), the percentage of patients who experienced symptoms within a month was 62% (adults) and 60% (children). The percentage of patients who were using ICSs was 34% (adults) and 20% (children).[11]

2.5. Deaths from Asthma[13]

According to the Vital Statistics of the Japanese Ministry of Health, Labour and Welfare, the number of patients (of all ages) who died from asthma has largely decreased in recent years. The number stopped decreasing at a rate of 4.5 to 5.0 per 100,000 population around 1975, then transiently increased in 1995, and decreased again after 1997, reaching its lowest point of 1.5 per 100,000 population (1,874 deaths) in 2012 (Fig. 2, 3). In particular, the number of patients who died from asthma at an early age has markedly decreased, and, on the other hand, about 90% of asthma deaths have occurred among elderly subjects aged 65 years or older (Fig. 4).

3. Patient Education and Physician-Patient Relationship

3.1. Educational Needs

It is required for patients to have a certain amount of knowledge in order to create a good relationship with medical professionals and to become capable of self-management. Sufficient patient education regarding asthma reduces the prevalence and mortality of asthma, improves the patients' QOL, and reduces medical expenses.[14] Effective education of patients includes the provision of a written self-management plan (action plan) that outlines the issues related to severity, self-management, and self-assessment of

Table 6 Classification of asthma severity based on the present treatment (adults)

	Present treatment step			
Patient's symptoms in the present treatment	Treatment step 1	Treatment step 2	Treatment step 3	Treatment step 4
Controlled † · No symptoms · No symptoms at night	Mild intermittent	Mild persistent	Moderate persistent	Severe persistent
Mild intermittent ‡ · Less than once a week · Mild and brief · Less than twice a month at night	Mild intermittent	Mild persistent	Moderate persistent	Severe persistent
Mild persistent § · Once or more a week, not every day · Once or more a month, disturbs everyday life and sleep · Twice or more a month at night	Mild persistent	Moderate persistent	Severe persistent	Severe persistent
Moderate persistent § · Every day · Requires short-acting inhaled β_2 agonist almost every day · Once or more a week, disturbs everyday life and sleep · Once or more a week at night	Moderate persistent	Severe persistent	Severe persistent	Most severe persistent
Severe persistent § · Frequently exacerbated even under treatment · Every day · Restrict everyday life · Frequently at night	Severe persistent	Severe persistent	Severe persistent	Most severe persistent

† Consider step-down after continued treatment for 3-6 months.
‡ Enhance treatment at each step.
§ Check compliance with treatment, and consider step-up as needed.

asthma, instructions on the use of medications, and timing of drug administration.[14]

3.2. Subjects
Education should be provided to patients, their families, neighbors, and caretakers for the elderly. It is also important for general physicians and medical staff to update their knowledge of asthma.

3.3. Contents
Since asthma is a chronic disease, the need for long-term management must be explained to patients. Patients, physicians, and medical staff should exchange information and discuss expected outcomes and any concerns regarding treatment. In addition, the aspects of asthma management listed in Table 11 should be discussed with patients. PEF monitoring is important to avoid and manage exacerbations. Patients should receive instructions on the measurement of PEF and the importance of PEF measurement (Table 12). Physicians should acquaint patients with the concept of prophylactic treatment and review the self-management plan with them if asthma gets worse.

3.4. Educators
Specialists in asthma cannot devote their whole time on patient education. Therefore, nonspecialists (general physicians) together with nurses, public health nurses, and pharmacists should also participate in education, and community-driven education is desired.

3.5. Places for Education
Education is a continuous task and is provided through events held by specialized institutions, health centers, patient support groups, and through distribution of various teaching materials. Ideally, medical personnel training on patient education should continue at health centers, school, and other

Table 7 Classification of asthma symptoms and exacerbation severity (adults)

Exacerbation severity†	Dyspnea	Exertion	Laboratory data§			
			%PEF	SpO_2	PaO_2	$PaCO_2$
Wheezing/chest tightness	Dyspnea on exertion	Almost normal	≥80%	≥96%	Normal	<45 mmHg
Mild (mild attack)	Dyspnea but no trouble with lying down	Slight dyspnea				
Moderate (moderate attack)	Dyspnea with trouble with lying down	Difficulty in moving Difficulty in walking	60-80%	91-95%	>60 mmHg	<45 mmHg
Severe (severe attack)	Dyspnea, cannot move	Abasia Difficulty in speaking	<60%	≤90%	≤60 mmHg	≥45 mmHg
Serious‡	Respiratory insufficiency Cyanosis Respiratory arrest	Anepia Akinesia Confusion, impaired consciousness, incontinence	Immeasurable	≤90%	≤60 mmHg	≥45 mmHg

† Determine exacerbation severity based on the extent of dyspnea, referring to other items. If symptoms of different exacerbation intensities coexist, use more severe one.

‡ Serious conditions, such as respiratory attenuation or arrest, anepia, impaired consciousness, and incontinence are regarded as emergency.

§ Refer to measured values after bronchodilator administration.

Table 8 Prevalence of bronchial asthma

	Age (yr)	Region	Year analyzed	Methods	*n*	Prevalence (%)
Children	6-12	11 Prefectures in Western Japan	1982	ATS-DLD	55,388	3.2
			1992		45,674	4.6
			2002		35,582	6.5
			2012		33,902	4.7
Adults	≥15	Fujieda, Shizuoka	1985	Original questionnaire	12,152	3.14
	≥15		1999	Original questionnaire + ATS-DLD	3,829	4.15
	20-79		2006	ECRHS	2,710	7.2

ATS-DLD, American Thoracic Society-Division of Lung Diseases; ECRHS, European Community Respiratory Health Survey.

facilities.

In Japan, information on asthma and educational activities are provided by various groups and associations such as the Japanese Society of Allergology (http://www.jsaweb.jp), Japanese Society of Pediatric Allergy and Clinical Immunology (http://www.jspaci.jp), Japan Allergy Foundation (http://www.jaanet.org), Independent Administrative Institution, Environmental Restoration and Conservation Agency of Japan (http://www.erca.go.jp), and the Japanese Council for Quality Health Care (http://minds.jcqhc.or.jp/index.aspx).

3.6. Quality of Life

The assessment of QOL is important in asthma management, as in other chronic diseases. QOL means general well-being, according to the Global Initiative for Asthma, and is useful for the analysis of morbidity. In addition to the Nottingham Health Profile and SF-36 Health Status Questionnaire, the Asthma Quality of Life Questionnaire and Asthma Health Questionnaire-33-Japan (AHQ-33J), prepared by the Japanese Society of Allergology, are often used. The AHQ-33J is reproducible, reliable, and useful for the assessment of social, familiar, and emotional factors.

Table 9 Prevalence of asthma by country, year and age group according to European Community Respiratory Health Survey

Country	Year	Age	Prevalence (%)
Japan	05	20-44	8.1
Australia	92-93	20-44	28.1
Australia Aborigine	90-91	20-84	11.1
UK	92-93	20-44	27.0
		20-44	30.3
Germany	92-93	20-44	17.0
Spain	92-93	20-44	22.0
France	92-93	20-44	14.4
USA	92-93	20-44	25.7
Italy	92-93	20-44	9.5
Iceland	92-93	20-44	18.0
Greece	92-93	20-44	16.0

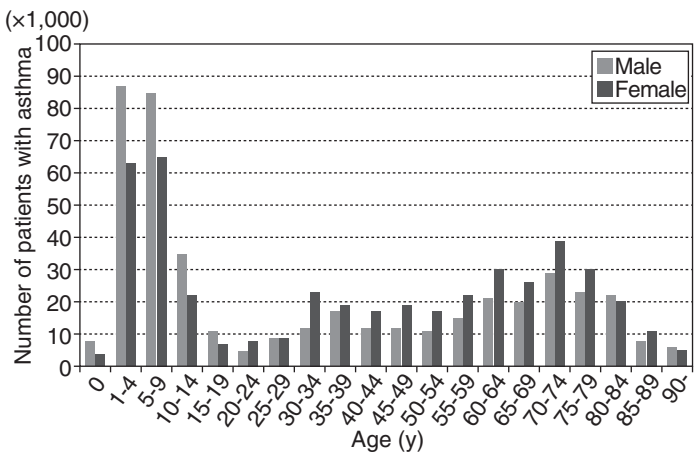

Fig. 1 Number of patients with asthma in Japan, by age and sex.

Table 10 Medical treatment rates for bronchial asthma in Japan

	Total	In-hospital	Outpatient
1999	132	12	120
2002	120	9	111
2005	122	7	115
2008	93	4	88
2011	107	3	103

per 100,000 population

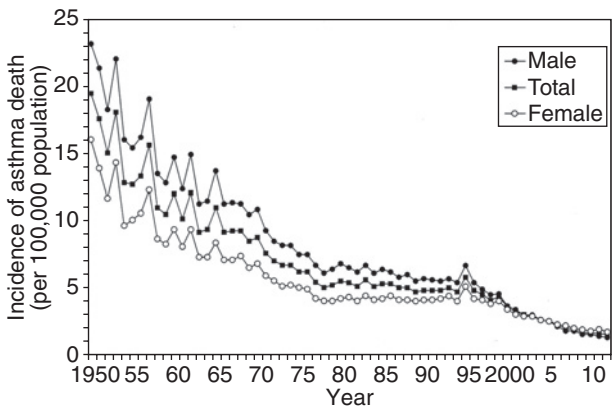

Fig. 2 Asthma mortality rates in Japan (1950-2012).

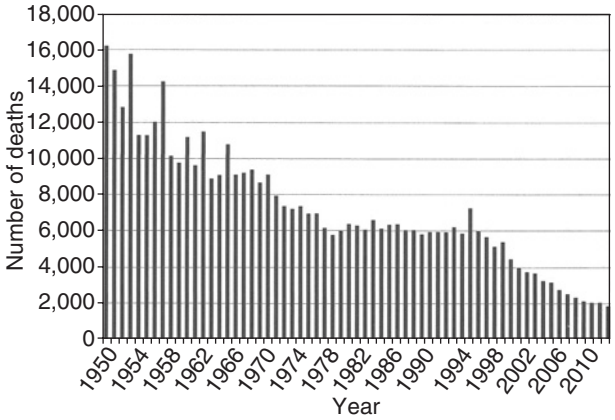

Fig. 3 Number of deaths from asthma in Japan (1950-2012).

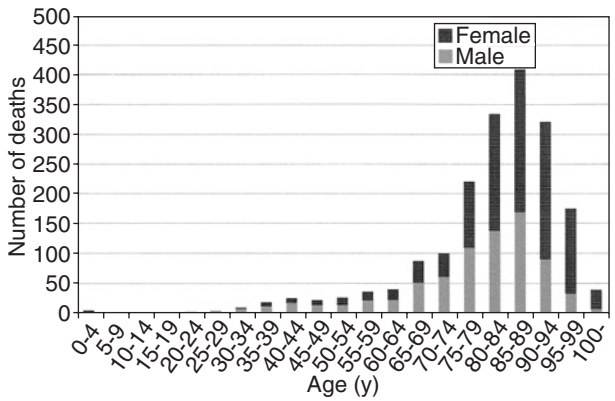

Fig. 4 Number of deaths from asthma by age in Japan (2012).

4. Asthma Medications

4.1. Asthma Medication Plan for the Long-Term Management of Adult Asthma

4.1.1. Agents

Asthma medications are divided into 2 types: controller agents used continuously for long-term management (controllers) and reliever agents used for a short period to treat asthma symptoms (relievers). They are administered via inhalation, oral route, injection (drip infusion, subcutaneous, or intramuscular), or skin patch. Inhalation using a pressurized metered-dose inhaler (pMDI) requires synchronized inhalation of a drug with its release and breath holding for drug deposition to the airways. A dry powder inhaler (DPI) requires enough inspiratory flow. Nebulizer inhalation is often used in patients with asthma attacks, children, or aged patients who cannot properly use a pMDI or DPI.

Table 11 Physician's instructions for patients with asthma

- Diagnosis
- Differences between reliever agents and controller agents
- How to use an inhaler
- Instructions for prophylaxis
- Signs of asthma exacerbation
- PEF monitoring
- How and when to visit clinics
- Self-management plan based on instructions

(1) Agents for long-term management (Controllers)

Agents to alleviate and eliminate asthma symptoms, and to normalize and maintain respiratory functions are called controllers. They are classified based on their mechanisms of action (Table 13).

a) Corticosteroids (steroids): corticosteroids are currently the most effective anti-inflammatory agents for asthma treatment.[15] The important mechanisms of action include (i) inhibiting infiltration of inflammatory cells into the lungs and airway,[16] and inhibiting the migration and activation of inflammatory cells; (ii) reducing vascular permeability; (iii) suppressing airway secretion; (iv) inhibiting airway hyperresponsiveness; (v) inhibiting cytokine production; (vi) promoting the effects of β_2-agonists[17]; and (vii) inhibiting arachidonic acid metabolism in cells other than human mast cells and the production of leukotrienes and prostaglandins. Four forms of steroids are available: for intravenous, intramuscular, oral, and inhaled use. Steroids used for long-term management of asthma are usually ICSs. An oral corticosteroid should only be used when control of asthma cannot be achieved with ICSs. An aqueous suspension of triamcinolone acetonide for an intramuscular injection should not be used because of its adverse effects.

ICSs have been shown to (i) reduce asthma symptoms; (ii) improve QOL and respiratory function; (iii) alleviate airway hyperresponsiveness[18]; (iv) inhibit airway inflammation; (v) reduce the frequency and severity of acute exacerbations[19]; (vi) reduce the maintenance dose of ICSs for a long period of time; (vii) reduce the medical expenses associated with asthma; (viii) inhibit airway remodeling; and (ix) reduce the rate of deaths from asthma. Furthermore, once asthma symptoms have developed, an early administration of an ICS (early intervention) will decrease the frequency of acute exacerbations.[20] However, asthma cannot be cured by the treatment and cannot be controlled if the treatment is discontinued.[18] In addition, poor compliance with ICS administration increases the number of emergency room visits and hospitalizations due to asthma exacerbations.

In step 4 of treatment (severe asthma), oral corticosteroids are used as long-term management agents

Table 12 Significance of peak expiratory flow monitoring

1. Diagnosis of asthma
Diurnal variation in peak expiratory flow is useful for elucidation of reversible airflow limitation
2. Accurate evaluation of airway obstruction and asthma severity
Patients with asthma often demonstrate discrepancy between symptoms and actual airway obstruction
3. Objective evaluation of the efficacy of asthma medications
4. Self-evaluation and management
Adequately educated patients can assess their own condition and the efficacy of drugs

Table 13 Controllers (agents for long-term management)

1. Corticosteroids
1) Inhaled corticosteroids
i) Beclomethasone dipropionate
ii) Fluticasone propionate
iii) Budesonide
iv) Ciclesonide
v) Mometasone furoate
2) Oral corticosteroids
2. Long-acting β_2 agonists
1) Inhalants
Salmeterol xinafoate
2) Patch
Tulobuterol
3) Oral medicines
Procaterol hydrochloride
Clenbuterol hydrochloride
Formoterol fumarate
Tulobuterol hydrochloride
Mabuterol hydrochloride
3. Combination inhaler of corticosteroid/long-acting β_2 agonist
1) Combination inhaler of fluticasone propionate/salmeterol xinafoate
2) Combination inhaler of budesonide/formoterol fumarate
3) Combination inhaler of fluticasone propionate/formoterol fumarate
4) Combination inhaler of fluticazone furate/vilanterol trifenatate
4. Leukotriene receptor antagonists
i) Pranlukast hydrate
ii) Zafirlukast
iii) Montelukast sodium
5. Theophylline sustained-release preparation
6. Anti-IgE antibody
Omalizumab
7. Antiallergics other than leukotriene receptor antagonists
1) Mediator antireleasers
Sodium cromoglicate, tranilast, amlexanox, repirinast, ibudilast, tazanolast, and pemirolast potassium
2) Histamine H_1 receptor antagonists
Ketotifen fumarate, azelastine hydrochloride, oxatomide, mequitazine, and epinastine hydrochloride
3) Thromboxane inhibitors
i) Thromboxane-A_2 synthesis inhibitor
Ozagrel hydrochloride
ii) Thromboxane-A_2 receptor antagonist
Seratrodast
4) Th2 cytokine inhibitor
Suplatast tosilate
8. Other agents and therapies (Chinese medicines, specific immunotherapy, and non-specific immunotherapy)

to complement ICSs, supplement adrenocortical functions, and reduce the levels of systemic inflammatory cells and inflammatory substances. However, oral corticosteroids are used for short-term intermittent administration, or are used at a minimum maintenance dose when continuous administration is required.

As shown in Table 14, ICSs commercially available in Japan in 2014 include fluticasone propionate (FP), budesonide (BUD), beclomethasone dipropionate (BDP), ciclesonide (CIC), mometasone furoate (MF) and fluticasone furoate. FP, BUD, and MF are also available as a DPI. On the other hand, pMDIs using hydrofluoroalkane (HFA) as a base are used for FP, BDP, and CIC administration. The mean particle sizes of these agents are 6 μm > FP-DPI > FP-HFA > BUD-DPI > MF-DPI > CIC-HFA = BDP-HFA > 1 μm. These agents are extensively dispersed in the airway, with smaller particles reaching further into the peripheral airway.[21] In addition, BUD inhalation suspension, inhaled using a nebulizer, has been recently introduced as a new formulation. A jet nebulizer is recommended for BUD inhalation suspension, but an ultrasonic nebulizer is unsuitable. To prevent adverse effects caused by BUD inhalation suspension, agents that come in contact with the face should be wiped off, and gargling and water intake are important. FF is available only as a combination with a LABA, vilanterol triphenylacetate, and is used once daily.

The dosage of ICSs is classified into a high dose

Table 14 Device for inhaled corticosteroids

	pMDI (Pressurized metered dose inhaler)	DPI (Dry powder inhaler)
BDP (beclomethasone dipropionate)	BDP-HFA (Qvar®)	None
FP (fluticasone propionate)	FP-HFA (Flutide® Air)	FP-DPI (Flutide® Diskus, Flutide® Diskhaler)
Combination inhaler with SM (salmeterol xinafoate)	FP/SM HFA (Adoair® aerosol)	FP/SM DPI (Adoair® Diskus)
Combination inhaler with FM (formoterol fumarate hydrate)	FP/FM (Flutiform®)	None
BUD (budesonide)	None	BUD-DPI (Pulmicort® Turbuhaler)
Combination inhaler with FM (formoterol fumarate hydrate)	None	BUD/FM (Symbicort® Turbuhaler)
CIC (ciclesonide)	CIC-HFA (Alvesco®)	None
MF (mometasone furoate)	None	MF-DPI (Asmanex® Twisthaler)
FF (fluticazone furate) Combination inhaler with VI (vilanterol trifenatate)	None	FF/VI-DPI (Relvar®Ellipta)

Table 15 Recommended doses of inhaled corticosteroids by treatment steps

Agent	Treatment steps 1-2 / Low dose	Treatment steps 2-3 / Medium dose	Treatment step 4 / High dose
BDP-HFA	100-200 μg/day	400 μg/day	800 μg/day
FP-HFA	100-200 μg/day	400 μg/day	800 μg/day
CIC-HFA	100-200 μg/day	400 μg/day	800 μg/day
FP-DPI	100-200 μg/day	400 μg/day	800 μg/day
BUD-DPI	200-400 μg/day	800 μg/day	1600 μg/day
BIS	0.5 mg/day	1.0 mg/day	2.0 mg/day
MF-DPI	100-200 μg/day	400 μg/day	800 μg/day

(the highest dose covered by health insurance), medium dose (half of the high dose), and low dose (half of the medium dose) (Table 15). ICSs are effective even at relatively low doses (e.g., 200 μg FP) in adults. However, if the dosage exceeds the high dose, further effects proportional to the dose cannot be achieved, and the risk of adverse effects is higher.[22] Thus, in controlling asthma, a more favorable outcome can be achieved by adding one or more controller other than ICSs rather than by simply increasing the dose of an ICS.[19] However, severe acute exacerbations can be alleviated by increasing an ICS dose.[19] Smoking reduces the effects of ICSs and impairs the respiratory function in patients with asthma.[23]

Apart from localized adverse effects, such as oropharyngeal candidiasis and hoarseness, ICSs have a few systemic adverse effects, including the effects on the eyes (cataract and glaucoma), skin (skin thinning and hemorrhage), bones (osteoporosis), and inhibitory effects on the hypothalamic-pituitary-adrenal function.[24] After inhalation, gargling is essential to alleviate oropharyngeal symptoms and reduce systemic absorption.

While conventional doses are generally acceptable, a careful follow-up is necessary when high doses are used. BUD-DPI, administered during early pregnancy, has not been reported to cause congenital malformation or to have any effects on the course of pregnancy.[25] The US Food and Drug Administration (FDA) has classified the safety of BUD-DPI in pregnant women as Category B. There is no evidence of an increased risk of respiratory tract infection, including tuberculosis, caused by ICSs in patients with asthma, and ICSs are not contraindicated in patients with active tuberculosis.

b) LABAs: β_2-agonists are potent bronchodilators that enhance airway mucus removal via epithelial cilia activation, and are administered via inhalation, patch, or oral route. As controllers, β_2-agonists should be

Table 16 Daily doses of combination inhaler of corticosteroids and long-acting β_2 agonists

	Low dose	Medium dose	High dose
FP/SM (DPI)	100 μg/dose, 1 dose b.i.d. 200 μg/100 μg	250 μg/dose, 1 dose b.i.d. 500 μg/100 μg	500 μg/dose, 1 dose b.i.d. 1000 μg/100 μg
BUD/FM† (DPI)	One dose b.i.d. 320 μg/9 μg	Two doses b.i.d. 640 μg/18 μg	Four doses b.i.d. 1280 μg/36 μg
FP/SM (pMDI)	50 μg/dose, 2 doses b.i.d. 200 μg/100 μg	125 μg/dose, 2 doses b.i.d. 500 μg/100 μg	250 μg/dose, 2 doses b.i.d. 1000 μg/100 μg
FP/FM (pMDI)	50 μg/dose, 2 doses b.i.d. 200 μg/20 μg	125 μg/dose, 2 doses b.i.d. 500 μg/20 μg	125 μg/dose, 4 doses b.i.d. 1000 μg/40 μg
FF/VI (DPI)	100 μg/dose, 1 dose s.i.d. 100 μg/25 μg	100 μg/dose, 1 dose s.i.d. 100 μg/25 μg or 200 μg/dose, 1 dose s.i.d. 200 μg/25 μg	200 μg/dose, 1 dose s.i.d. 200 μg/25 μg

FP, fluticasone propionate; SM, salmeterol xinafoate; BUD, budesonide; FM, formoterol fumarate; FF, fluticazone furate; VI, vilanterol trifenatate.

† Indication in a delivered dose.

used concomitantly with ICSs. When a LABA is combined with an ICS, the steroid increases the number of β_2-receptors, and the β_2-agonist promotes the nuclear translocation of steroid receptors, thereby enhancing the steroid action. Furthermore, the combined therapy of an ICS and LABA can allow clinicians to reduce the dose of an ICS[26] and increase the number of patients with well-controlled asthma. The combination of an ICS and LABA is more effective than an ICS with sustained-release theophylline.[27]

Salmeterol xinafoate is an inhaled LABA that cannot be used alone for the treatment of asthma[28]; however, it has high synergistic effects when combined with an ICS.[29] Conventional oral LABAs include procaterol hydrochloride, clenbuterol hydrochloride, and mabuterol hydrochloride. A tulobuterol patch, which was developed in Japan, is a long-acting agent with a bronchodilator action that continues for 24 h. It is useful in patients for whom inhalation and oral administration are difficult. Its clinical usefulness when used concomitantly with an ICS has been reported.[30] LABAs have a high safety profile in any formulation. However, adverse effects include tremor, palpitation, and tachycardia, and occur most frequently for oral agents, followed by patches, and inhaled agents. When adverse effects are observed, the dose should be reduced or administration should be discontinued according to the complaint. Serious adverse effects include a decreased serum potassium level. LABAs should be used more carefully in patients with ischemic heart disease, hyperthyroidism, and diabetes mellitus. In addition, the adverse effects of the tulobuterol patch include skin itching or rash (or both) around the patch area.

c) Combination agents of ICS and inhaled LABA (ICS/LABA) (Table 16): In Japan, fluticasone/salmeterol, BUD/formoterol, and new drugs such as fluticasone/formoterol and fluticasone furoate/vilanterol are currently available as combination agents of ICS/LABA, which are more effective than when inhaled separately.[31] They have the following advantages: (i) the number of inhalations can be reduced; (ii) excellent compliance can be achieved; and (iii) the use of LABAs alone can be avoided. Recently, it has been reported that mild asthmatic patients can be controlled by combination agents used once daily.[32] Furthermore, the rescue use of BUD/formoterol instead of a short-acting β_2-agonist (SABA) can improve asthma symptoms and reduce the rate of asthma exacerbations.[33] However, it is important to alleviate asthma symptoms and normalize and maintain respiratory functions for long-term management by the regular use of ICSs and combination agents. According to the 2010 FDA recommendations, asthma treatment should be based on the assessment of the control level when using these combination agents.[34] If the simultaneous use of a LABA can be discontinued when asthma is well controlled, a switch to an ICS alone can be made. However, it remains controversial whether a continuing use of combination agents can reduce the rate of severe exacerbations compared to ICSs alone after a good control of asthma is achieved.[35,36]

d) LTRAs: leukotrienes (LT) C_4, D_4, and E_4 are called cysteinyl LTs (CysLTs), and their respective receptors are $CysLT_1$, $CysLT_2$, and $CysLT_3$. A currently available LTRA is a $CysLT_1$ receptor antagonist. Three types of LTRAs are available: pranlukast hydrate, zafirlukast, and montelukast. LTRAs have a bronchodilator action and inhibit airway inflammation, resulting in a significant improvement of asthma symptoms, respiratory function, inhalation frequency

of as-needed inhaled β2-agonist, airway inflammation, airway hyperresponsiveness, dosage of ICSs, asthma exacerbations, and patients' QOL.[37-39] LTRAs are useful as agents used concomitantly with an ICS in patients with asthma that cannot be completely controlled even with a medium dose of an ICS, because the additional administration of LTRAs is as effective as a double dose of an ICS.[40] Compared with LABAs, LTRAs used in combination with an ICS are less effective in improving symptoms and respiratory function and are almost equivalent in preventing exacerbations.[41] LTRAs are useful for long-term management of patients with asthma complicated by allergic rhinitis, exercise-induced asthma (EIA), and AIA. Generally, LTRAs alone are less effective compared with low doses of ICSs, whereas the effects of LTRAs plus ICSs are reported to be the same as those of LABAs plus ICSs in steroid-naïve asthmatic patients.[32,42]

In some patients, respiratory function improves early after the oral administration of an LTRA (at several hours at the earliest, on the following day at the latest); however, anti-inflammatory effects develop later. Thus, efficacy is generally judged after 2 to 4 weeks after administration. While more reports have been published on EGPA in patients who have received an LTRA than in those who have received other antiasthmatic drugs, no conclusion has been reached as to whether an LTRA is directly involved in the onset of EGPA.[43] LTRAs are generally safe drugs, although zafirlukast should be used with caution because it may cause severe hepatopathy and interact with other agents, such as warfarin, since it is metabolized by CYP2C9. LTRAs seem to be relatively safe for pregnant women.

e) Sustained-release theophylline: sustained-release theophylline is a long-acting bronchodilator with anti-inflammatory effects. It inhibits airway infiltration of lymphocytes and eosinophils,[44] T-cell proliferative response, cytokine production, apoptosis induction of eosinophils,[45] and recovery of steroid sensitivity through histone deacetylase reactivation.[46] While sustained-release theophylline is clinically less effective than ICSs, when used in combination with low-to-medium doses of an ICS, the same effects as those obtained with an increased dose of an ICS can be achieved.[47] However, as a concomitant drug with ICSs, sustained-release theophylline at a dose of 300 to 400 mg/day improved airway obstruction to a lesser extent than LABAs did[27] and to a comparable (the same or slightly lesser) extent than LTRAs did.[48] The effective safety range of theophylline is rather narrow, and the serum theophylline level varies depending on various factors (age, smoking, drug interaction, etc.); thus, monitoring of its serum level may be useful to avoid adverse effects. Anti-inflammatory effects are obtained at a serum theophylline level of 5 to 10 μg/mL, and, importantly, a bronchodilator action is achieved in a concentration-dependent manner. No serious adverse effects have been noted at serum theophylline concentrations of up to 20 μg/mL. Monitoring the peak serum theophylline level is difficult, thus the target level is from 5 to 15 μg/mL. The adverse effects of theophylline include gastrointestinal symptoms such as nausea and vomiting at initial oral administration. Toxic symptoms caused by increased serum theophylline levels include nausea and vomiting at first, and may progress to tachycardia and arrhythmia. In the most severe cases, convulsions may occur that can lead to death. In pregnant women, no effect of theophylline has been noted on the frequency of fetal disorders as far as appropriate serum levels are maintained.

f) Anti-IgE antibody: omalizumab is a humanized antihuman IgE monoclonal antibody that binds to IgE to inhibit the binding between IgE and the high affinity IgE receptor, thereby decreasing the expression of the high affinity IgE receptor on tissue mast cells and circulating blood basophils. Anti-inflammatory effects have been reported, such as a reduced number of eosinophils, T cells, B cells, and Th2 cytokine-positive cells in the sputum and airway tissue and decreased serum interleukin (IL)-5 and IL-13 levels.[49,50]

The dose and frequency of administration are determined based on a dosage conversion table according to patient weight and serum IgE level (30-1,500 IU/mL) to reduce serum free IgE levels to 10 IU/mL or lower. Omalizumab has the following effects in patients with a poor control of asthma even despite treatment with a high dose of ICS: (i) preventing exacerbation; (ii) reducing the freguency of asthmatic symptoms; (iii) improving QOL; and (iv) reducing a steroid dose.[51] Omalizumab should be used as a therapeutic agent in step 4 treatment for severe persistent asthma, sensitized to perennial inhalation antigens (mites, animals, fungi, etc.). It is effective in about 60% of the patients. At 16 weeks after administration, therapeutic effects are comprehensively judged based on the frequency of exacerbations, QOL, respiratory function, and other variables, to determine whether treatment should be continued.[52] In a Japanese clinical study, the PEF rate, FEV_1, and the frequency of exacerbations were significantly improved in poorly controlled patients with the concomitant use of a high-dose ICS and one or more controller agents. It is unknown whether treatment can be discontinued after long-term administration.

The major adverse effects of omalizumab are pain and swelling at the injection site. An anaphylactic reaction, reported as a serious adverse effect in 0.1% to 0.2% of the patients overseas, could develop within 2 h after administration (about 70% of the episodes), but some reactions have been reported to occur after 24 h. Symptoms may develop both in the initial stages of administration and after longer use. The drug should be administered with caution because EGPA may develop due to the reduced amount of systemic

steroids. No teratogenicity has been reported, and the antibody is safe for pregnant women, although it penetrates the placenta.

g) Antiallergic agents other than LTRAs: antiallergic agents include either mediator-release suppressants or mediator inhibitors, and are effective in 30% to 40% of the patients with mild-to-moderate atopic asthma, although an administration period of 4 to 6 weeks or longer is needed to determine their efficacy. Safety of oral antiallergic agents in fetuses during pregnancy has not been demonstrated.

Mediator-release suppressants: the main effect of mediator-release suppressants is inhibiting the release of chemical mediators from mast cells. Long-term use of inhaled disodium cromoglycate (DSCG) inhibits airway inflammation in patients with atopic asthma.[53]

Histamine H_1-antagonists: the main effect of these agents is to antagonize the action of histamine through H_1-receptors. The antagonists are beneficial for asthma accompanied by allergic rhinitis or atopic dermatitis. Adverse effects may include sleepiness and malaise.

Thromboxane-A_2 inhibitors/antagonists: thromboxane-A_2 synthesis inhibitors and thromboxane-A_2 receptor antagonists inhibit airway inflammation, improve airway hyperresponsiveness, and improve impaired mucociliary transport. Their adverse effects include a tendency for increased bleeding, thus we should be cautious about the concomitant use of other agents with inhibitory effects on platelet aggregation.

Th2 cytokine inhibitor: the major effects of a Th2 cytokine inhibitor, suplatast tosilate, are inhibition of IL-4 and IL-5 production from Th2 cells, inhibition of eosinophil infiltration into the airway mucosa, and alleviation of airway hyperresponsiveness in patients with asthma.[54] The inhibitors allow to reduce the dose of an ICS.[55]

h) New therapeutic agents: a long-acting anticholinergic drug (a long-acting antimuscarinic agent, LAMA) is the first-line drug in patients with chronic obstructive pulmonary disease (COPD) and is useful in asthmatic patients with COPD (asthma-COPD overlap syndrome). When a LAMA is used in combination with an ICS in asthmatic patients without COPD, its effect is comparable to that of a LABA.[56] Antibodies against IL-5 and IL-13 are being developed for patients with severe asthma.[57-59]

(2) Reliever agents

a) SABAs: SABAs are regarded as reliever agents. Inhalation therapy using a pMDI, DPI, and nebulizer shows a comparable or even higher bronchodilator action compared with oral administration. However, there are a few adverse effects such as stimulation of the cardiovascular system, skeletal muscle tremor, and hypokalemia, which can be reduced using a spacer. The increasing need for the use of a SABA may be regarded as an exacerbation, and inhalation can be repeated as needed. The use of a SABA as a reliever 5 times or more daily means that controller agents are necessary. If the effects are not satisfactory after repeated inhalation every 20 min for 1 h, medical consultation is needed. SABAs are effective in the prevention of allergen-induced asthma or EIA and treatment of exacerbations.

b) Oral corticosteroids: for acute asthma attacks (moderate exacerbations), an oral corticosteroid, together with a SABA, needs to be administered for a short period (about 1 week). Prior short-term treatment of asthma symptoms (usually less than 1 week) with a medium or high dose of an oral corticosteroid (approximately 0.5 mg/kg of prednisolone) prevents acute exacerbations, decreases emergency visits and hospital admissions, and reduces the restrictions on daily life due to asthma attacks. In short-term treatment (less than 2 weeks), a sudden dose reduction or discontinuation of treatment will not result in adrenocortical insufficiency (steroid withdrawal syndrome). Patient compliance with the treatment regimen should be reassessed.

c) Theophylline: A single use of oral aminophylline is used as a reliever agent, and its dose depends on its serum levels.

d) Inhaled anticholinergics: inhaled anticholinergics have additive effects with β_2-agonists on acute exacerbations. They are especially useful in elderly patients with asthma -COPD overlap syndrome.

(3) Other agents and therapies

a) Chinese herbal medicines: selection of an agent is based on the patient's physical constitution, strength, and response to disease at the time of administration; the empirical process helps distinguish between responders and nonresponders before administration.

b) Other agents: expectorants such as carbocisteine and fudosteine may facilitate expectoration, and macrolides may inhibit neutrophilic inflammation observed in some asthmatic patients. However, accumulated evidence is not sufficient to recommend any of these agents.

c) Specific immunotherapy: allergen-specific immunotherapy is indicated in patients with symptoms caused by the relevant allergens that cannot be avoided, patients with allergic rhinitis, and asthmatics who desire tapering medication or who are intolerant to some drugs owing to adverse effects. This therapy induces regulatory T cells, resulting in the inhibition of cytokine production from Th2 cells and chemical mediator production from mast cells to improve eosinophilic airway inflammation and airway hyperresponsiveness.[60]

Table 17 Assessment of asthma control

	Well-controlled (meet all the criteria)	Insufficiently-controlled (meet 1 or 2 criteria)	Poorly-controlled
Asthma symptoms (in the daytime or at night)	None	Once or more a week	Meet 3 or more criteria of insufficient control
Use of reliever	None	Once or more a week	
Limitation of activities, including exercise	None	Restricted	
Lung function (FEV_1 and PEF)	Predicted value or ≥80% of the best value	Predicted value or <80% of the best value	
Diurnal (weekly) variation in PEF	<20%	≥20%	
Exacerbation	None	Once or more a year	Once or more a month †

† Determine patients with one or more exacerbations a month as being poorly controlled, even if they do not meet the other criteria.

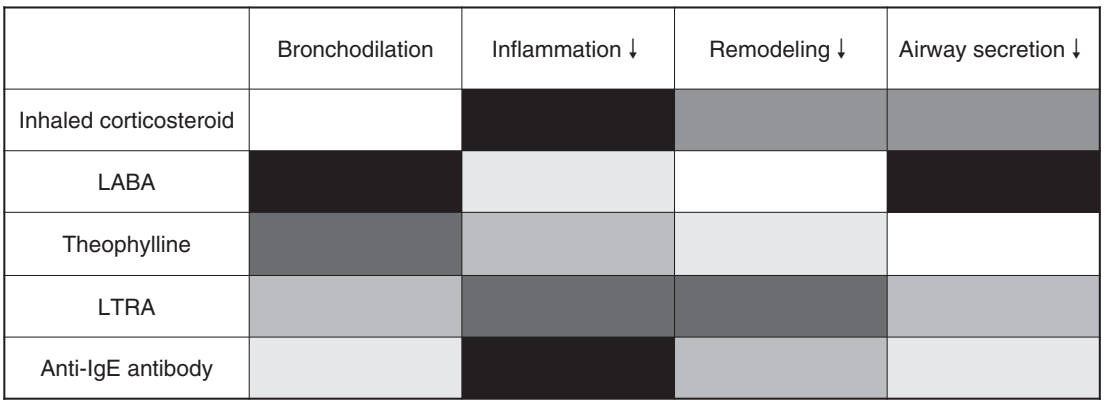

Fig. 5 Effects of individual agents on asthma symptoms in long-term management.
LABA, long-acting β_2-agonists; Theophylline, sustained-release theophylline preparation; LTRA, leukotriene receptor antagonists. The effect of each drug on asthma symptoms is reflected by the five shades of gray.

4.1.2. Stepwise treatment plan

(1) Aim of asthma treatment

The aim of asthma treatment is to achieve normal respiratory function in the absence of symptoms or adverse effects. In patients with airway remodeling, normal respiratory function cannot be restored; thus, it can be assessed based on their best values. The control status is determined as shown in Table 17, with the aim to achieve asthma control.

(2) Principles of treatment

A better relationship between patients and physicians largely depends on the effects of initial treatment, which focuses on the improvement of asthma symptoms. Apart from using therapeutic agents for asthma, it is important to avoid and eliminate sensitizing allergens (mites, fungi, cockroaches, animals, pollen, and others) and exacerbating factors such as passive and active smoking and excessive fatigue. Management of concomitant diseases, such as allergic rhinitis and COPD, is also important.

Asthma treatment is divided into 4 treatment steps based on asthma severity. The steps are outlined in the following section. The aim of drug therapy is to achieve the maximum effect using the minimum number of drugs. Symptoms at the initiation of therapy, those at consultation, and therapeutic situation are comprehensively evaluated to determine the appropriate treatment step. Each controller drug has a characteristic spectrum of effects based on the evidence of their basic mechanisms of action and clinical efficacy (Fig. 5). It would be valuable to consider the features of each drug when multiple drug therapy is necessary.

(3) Four treatment steps in asthma (Table 5)

Treatment is stepped up when asthma symptoms deteriorate or sufficient control cannot be achieved with current pharmacotherapy. Maintenance therapy is determined on the basis of asthma symptoms and PEF. When asthma attack occurs during long-term management, a SABA should generally be used as a

reliever. In steps 2 and 3 of asthma treatment, if patients are treated with a combination of BUD and formoterol as a controller, its use as a reliever should not exceed the maximum number of inhalations for each use and day as shown in the legend of Table 5. Caution should be taken when stepping the treatment down to prevent the aggravation of symptoms, and the patient should be informed about the treatment against exacerbations during dose reduction.

a) Step 1 treatment: one (or no) controller agents plus a reliever agent. A SABA without controllers may be administered only to patients with rare asthma symptoms (less than once a month), in whom no long-term management is needed. It should be emphasized that many patients with asthma underreport their symptoms. For patients who develop symptoms once or more a month, a low dose of an ICS is recommended as a controller agent.[20] If ICSs cannot be used, or adverse effects develop after inhalation, LTRAs[37] or sustained-release theophylline[44] can be used, but their anti-inflammatory activities are inferior to those of ICSs.

b) Step 2 treatment: two controller agents plus a reliever agent. In addition to ICSs (low-to-medium dose), a LABA,[28,29] LTRA,[41,61] or sustained-release theophylline[47] can be used. A low-to-medium dose of an ICS/LABA can also be used.[62] LTRAs should be considered mainly in patients with coexisting allergic rhinitis and sympathetic nerve stimulation caused by a LABA or theophylline. Depending on disease conditions, antiallergic agents other than LTRAs can be simultaneously used.

c) Step 3 treatment: Two or more controller agents plus a reliever agent. In addition to an ongoing treatment with an ICS (medium-to-high dose), a LABA and LTRA, or a LABA with sustained-release theophylline, or a LABA with both an LTRA and sustained-release theophylline, are used. A medium-to-high dose of ICS/LABA can also be used.[62]

d) Step 4 treatment: controller agents plus a reliever agent plus additional therapy. In addition to continuous administration of an ICS (high dose), a LABA, LTRA, or sustained-release theophylline is used. A high dose of ICS/LABA can also be used.[62] When good control of asthma cannot be achieved even when using a high dose of an ICS in combination with other drugs, anti-IgE antibody (omalizumab) is effective in poorly controlled patients sensitized to perennial allergens, whose serum total IgE level is within a therapeutic target range (30-1,500 IU/mL).[51] The dose of an anti-IgE antibody is determined based on the total IgE value and body weight, using a dosage conversion table. Its effects are evaluated 16 weeks after administration, and if effective, administration is continued. Oral corticosteroids should be intermittently administered for a short period to avoid prolonged administration wherever possible. Specifically, about 0.5 mg/kg or the equivalent amount of prednisolone is administered for a short period (usually less than 1 week), and a high-dose ICS is subsequently used. In patients with insufficient asthma control, who need prolonged administration of an oral corticosteroid, a shorter-acting oral corticosteroid (prednisolone) can be administered every day or every other day in the morning to maintain the minimum dose (5 mg). Caution should be taken when switching from long-term administration of an oral corticosteroid to a high-dose ICS because of possible adrenal insufficiency.

(4) Practical application

a) Selection of treatment steps: in untreated patients, treatment step is determined on the basis of asthma symptoms and measurement of pulmonary function, including such parameters as PEF and FEV_1 (Table 4). Specifically, treatment steps are selected as follows: (i) step 1 treatment for mild intermittent symptoms; (ii) step 2 treatment for mild persistent symptoms; (iii) step 3 treatment for moderate persistent symptoms; and (iv) step 4 treatment for severe persistent symptoms. In patients who have already received drug therapy such as controllers, which is often the case, the treatment step should be determined according to Table 6. It is important to maintain good control of asthma throughout treatment (Table 17). If asthma symptoms are not controlled well, intensification of treatment should be considered. When symptoms occur less than once a week, intensification of treatment within the same treatment step should be considered. When asthma symptoms occur every week or every day, one step-up or two step-ups are required for good control. In patients receiving drug therapy, a step-down should be considered if asthma control continues for 3 to 6 months, based on the assessment of the control status presented in Table 17.

b) Useful considerations for monitoring asthma management during follow-up are summarized as follows.

i) Spirometry: the measurement of pulmonary function (airflow limitation) is important to determine the severity of asthma and evaluate effectiveness of treatment.[63] The degree of airflow limitation is determined by reduction in FEV_1, $\%FEV_1$ ($\%FEV_1 = FEV_1/\text{forced vital capacity} \times 100$), and PEF. The decreased values of V_{50} and V_{25} and increased values of the V_{50}-to-V_{25} ratio are useful for early diagnosis of peripheral airway diseases.

ii) PEF: to evaluate the degree of airflow limitation objectively every day, monitoring of PEF is recommended. It is particularly beneficial in asymptomatic patients or in those with frequent exacerbations. It can also be used to determine antigens or exacerbation factors. Diurnal variation of PEF is correlated with the degree of airway hyperresponsiveness. Large daily variation of PEF signifies increased air-

way hyperresponsiveness. Thus, it becomes a good marker of asthma control.[64-66]

iii) Asthma diaries and questionnaires: asthma diary, Asthma Control Questionnaire, and Asthma Control Test are useful for evaluation of asthma control.[67-69]

iv) Percentage of sputum eosinophils: if spontaneous sputum is not obtained, sputum can be induced by inhalation of hypertonic saline. To avoid airway contraction by hypertonic saline inhalation, the patient should inhale a SABA prior to hypertonic saline inhalation. Several reports have demonstrated that the management of eosinophil-oriented asthma is superior to that of symptom-oriented asthma in reducing asthma exacerbations.[70-72]

v) Airway hyperresponsiveness: using the threshold values of airway hyperresponsiveness, better management can be achieved compared with the management guided by conventional symptoms and pulmonary function.[73] Because airway hyperresponsiveness can be measured only in specialized centers, the general clinical usefulness of the airway hyperresponsiveness test is limited.

vi) Measurement of FeNO: exhaled NO is released from inducible NO synthase in airway epithelial cells. It reflects the degree of airway eosinophilic inflammation. Because the measurement of FeNO is easy and noninvasive, it is useful for the diagnosis of asthma and monitoring of airway inflammation. Moreover, high levels of FeNO indicate good responsiveness to steroid treatment.[74-79]

vii) Other parameters: eosinophil count in the peripheral blood and specific IgE antibodies are useful for the diagnosis of asthma. Blood theophylline concentration or corticosteroid levels are important to monitor patients receiving asthma pharmacotherapy. When asthma is exacerbated, respiratory failure should be assessed by pulse oximetry and arterial blood gas analysis. In such cases, blood tests, chest radiograph, and electrocardiogram should be performed to exclude other diseases.

(5) Management of difficult-to-treat patients

Uncontrolled or partly controlled patients need adequate instruction regarding daily medication, inhalation technique, and management for acute exacerbation and are provided with an asthma diary that records the doses and timing of asthma medications. Patients with worsening symptoms are instructed to follow an emergency manual immediately. In addition, patients are acquainted with dose reduction strategies. Furthermore, in case of acute exacerbation, they should have contact information handy, addresses of emergency hospitals, and an "asthma notification card," which enables treating physicians and other physicians to administer emergency treatment.

Early referral to a specialist is recommended for patients with underlying diseases such as AIA, EPGA (CSS), other systemic vasculitis, and allergic bronchopulmonary aspergillosis, because, in addition to the above treatment steps, a continuous administration of a systemic steroid or immunosuppressant may be needed.

a) AIA: About 10% of the patients with adult asthma suffer from an asthma attack immediately or within 1 h after the administration of nonsteroidal anti-inflammatory drugs (NSAIDs), which have aspirin-like effects. This type of asthma is called "aspirin-induced asthma" and about 50% of the cases are refractory asthmatic patients. They often have nasal polyp and eosinophilic sinusitis. Not only aspirin but also acidic NSAIDs induce severe asthma attack; therefore, a physician instructs patients not to use NSAID-containing oral medicines, suppository, patches, and ointments for long-term management. A physician should consider treatment of the complicating nasal polyp and eosinophilic sinusitis.

In treating acute exacerbations, caution should be exercised for induction of asthma attack by some types of steroids. When administration of systemic steroid is needed in an asthma attack, oral steroids or intravenous infusion of steroid phosphate esters are recommended.

b) EPGA (also known as CSS): EPGA is characterized by asthma, increase of eosinophil levels in the blood and tissues, and polyangiitis of many organs.[79] The treatment of choice in EPGA is systemic steroids. Poor-prognosis factors (five-factor score) is proposed.[80] In patients with severe asthma and cardiac disease or in steroid-resistant patients, cyclophosphamide is used in combination with systemic steroids. Sometimes, an intravenous infusion of immunoglobulin is administered in treatment-resistant patients with nerve or cardiac disorder.

c) ABPA: ABPA is a disease characterized by asthma and lung infiltration induced by abnormal immunoreaction against *Aspergillus*, resulting in irreversible destruction of the airway architecture (bronchiectasis) and lung fibrosis. In addition to asthma treatment, systemic steroids are required.[81] When the dose of systemic steroids cannot be reduced, an administration of antifungal drug, itraconazole, should be considered.

d) Gastroesophageal reflux disease (GERD): GERD is a complicating disease in asthmatic patients, and the symptoms are frequently seen in uncontrolled asthmatic patients. Administration of theophylline or oral steroids sometimes exacerbates GERD. GERD is treated with proton-pump inhibitors. Treatment with proton-pump inhibitors does not necessarily improve asthma control in patients with uncontrolled asthma without the symptoms of GERD.

e) Asthma with allergic rhinitis: asthma may be significantly complicated by allergic rhinitis. Active complicating allergic rhinitis in asthmatic patient should

Table 18 Factors influencing serum theophylline level

Decreased clearance (increases serum level)
- Aging (50 years or older) and extreme obesity
- Complications, such as hepatopathy, heart failure, virus infection, and fever
- Agents: allopurinol, macrolides (erythromycin, clarithromycin, and roxithromycin), cimetidine, diazepam, new quinolones (ENX, CPFX, and TFLX), thiabendazole, propranolol (contraindicated for asthma), etc.
Increased clearance (decreases serum level)
- Smoker (who smoke ≥15 cigarettes/day)
- Agents: barbituric acid, antiepileptics (carbamazepine and phenytoin), rifampicin, isoproterenol, etc.

be simultaneously treated.[82] Pharmacotherapy for allergic rhinitis may alleviate asthma symptoms and improve airway hyperresponsiveness.[83,84] In addition, an LTRA improves the clinical symptoms in this patient group. Concomitant use of an LTRA is more effective in improving airway obstruction due to asthma than doubling the dose of an ICS.[85]

f) Asthma with COPD: COPD is an important coexisting disease, requiring caution in differential diagnosis in elderly patients with asthma. COPD is also an important disease as comorbidity. Particularly, elderly patients with asthma, who have a smoking history, should be diagnosed. Since long-acting inhaled anticholinergics are recommended for COPD, a concomitant use of inhaled tiotropium is preferable in elderly patients with asthma complicated by COPD. A therapeutic agent should be chosen considering that a combination inhaler device of a corticosteroid and a LABA is also effective for COPD.

4.2. Management of Acute Exacerbations in Adults

4.2.1. Therapeutic agents

(1) Inhaled β_2-agonists

Better therapeutic effects can be obtained by repeated administration of a small dose (1 to 2 puffs at a time using a portable pMDI) for a fixed period than by single administration of a high dose.[86] For acute asthma symptoms, a SABA is inhaled every 20 min for the first hour and subsequently every hour until improvement is noted. Inhalation using a spacer is more effective[87] because it causes less adverse effects. If adverse effects such as marked tremor and palpitation develop, the inhalation should be discontinued. A nebulizer is effective in allowing continued inhalation coupled with oxygen. Adding an inhaled anticholinergic may provide an additive bronchodilator action.[88]

(2) Subcutaneous injection of adrenaline (0.1%)

Catecholamine formulation (adrenaline, 0.1%) may be administered when no sufficient effects can be obtained with an inhaled β_2-agonist, but caution should be exercised because arrhythmia, cardiac arrest, and other adverse effects may develop. Subcutaneous injection of adrenaline (0.1%, 0.1-0.3 mL) provides a bronchodilator action through the relaxation of the bronchial smooth muscles (β effect) and the removal of airway mucosal edema (α effect). Although the administration can be repeated every 20 to 30 min, pulse rate monitoring is desirable and it should be kept at a rate of 130/min and lower. This agent is contraindicated in patients with complications such as arteriosclerosis, hyperthyroidism, diabetes mellitus, severe arrhythmia, psychoneurosis, and glaucoma (except for open-angle [simple] glaucoma). In addition, caution should be exercised for the following agents because of contraindication for concomitant use with adrenaline: i) inhaled halogen-containing anesthetics such as halothane (they carry an increased risk of tachycardia and ventricular fibrillation); ii) antipsychotics (butyrophenones, phenothiazines, iminobenzyls, zotepine, and risperidone) and α-blockers (they may result in hypotension due to epinephrine reversal); iii) catecholamine formulation, such as isoproterenol, and adrenergic agents are principally contraindicated unless in emergent cases such as resuscitation (concomitant use may develop arrhythmia, and, in some cases, cardiac arrest); iv) a tulobuterol patch may be concomitantly used with caution; however, a concomitant use with fenoterol is contraindicated.

(3) Theophylline

The effective serum concentration of theophylline is from 8 to 20 μg/mL (<15 μg/mL in children), and adverse effects will occur when exceeding this range. Intravenous infusion of aminophylline (6 mg/kg) has a bronchodilator action and positive effects on the respiratory drive and respiratory muscles; thus, it is effective in treating acute asthma attacks.[89] Aminophylline has additive effects for β_2-agonists,[89] and its use decreases hospitalization rates due to asthma attacks. Safer and more sufficient administration can be achieved by monitoring the level of serum theophylline. For safety reasons, initial administration is conducted with 6 mg/kg of aminophylline (250 mg/ampule) in 200 to 250 mL of isotonic fluid, and the first half is infused over 15 min and the other half over 45 min when theophylline was insufficiently administered before exacerbation and theophylline clearance

Table 19 High-risk group of asthma exacerbation

High-risk group meet any one of the following criteria:
1. Receiving systemic steroid administration, or immediately after the administration was discontinued.
2. History of hospitalization due to asthma attack in the past 1 year
3. Emergency visit due to asthma attack in the past 1 year
4. Tracheal intubation due to asthma attack in the past
5. Coexisting mental disorder
6. Noncompliance with asthma treatment plan
7. Not using an inhaled corticosteroid
8. Excessive use of short-acting β_2 agonist

was normal. If 600 mg or more of sustained-release theophylline is administered daily, serum theophylline level is 8 μg/mL or higher, or reduced clearance is suspected, the dose of aminophylline should be reduced to half or less. If toxic symptoms of theophylline (headache, nausea, vomiting, tachycardia, arrhythmia, and others) occur during administration, the intravenous infusion must be discontinued immediately. Even if subjective symptoms are improved after intravenous infusion, patients should rest for about 30 min. Serum levels of theophylline should be monitored during treatment wherever possible.

Caution should be exercised for intoxication in the presence of factors affecting theophylline clearance, as shown in Table 18. For continuous administration of aminophylline, one ampule (250 mg) of aminophylline is added to 500 mL of maintenance infusion fluid to be used in continuous intravenous drip infusion for 5 to 7 h (about 0.6-0.8 mg/kg/h) according to the individual's physical constitution. The speed of intravenous drip infusion should be adjusted to achieve 8 to 20 μg/mL of serum theophylline levels. If toxic symptoms of theophylline occur during administration, the intravenous drip infusion must be slowed down or discontinued, and overdose should be ruled out by measuring the level of theophylline. PaO_2 may transiently fall during continuous administration of aminophylline, and when hypoxemia develops, oxygen should be used (1-2 L/min with nasal cannulas).

(4) Corticosteroids

Corticosteroids (steroids) are recommended for patients with exacerbated symptoms, insufficient bronchodilator action, moderate or severe exacerbations, and for those who are already receiving steroids.[90] The initial dose is set at 200 to 500 mg of hydrocortisone or 40 to 125 mg of methylprednisolone,[90] with subsequent intravenous drip infusion of 100 to 200 mg of hydrocortisone or 40 to 80 mg of methylprednisolone every 4 to 6 h as needed. However, considering the time until clinical effects of steroids develop (approximately 4 h) and safety, intravenous drip infusion for about 30 to 60 min is recommended as initial administration.

When symptoms become worse after the initial infusion of hydrocortisone or methylprednisolone, steroid-induced exacerbation should be considered and the steroid should be changed to another hydrocortisone or another steroid (dexamethasone or betamethasone). In patients with AIA, steroid phosphate esters (i.e., dexamethasone or betamethasone) should be used because steroid succinate esters may induce worsening in 40% to 60% of patients.[91]

Systemic steroid administration is indicated for patients with:

- moderate-to-severe exacerbations.
- history of a severe asthma attack requiring systemic steroid administration.
- history of an advanced severe asthma attack requiring hospitalization.
- significant risk factors of exacerbations (Table 19).

(5) Oxygen

Oxygenation can be initiated in patients with severe dyspnea or PaO_2 of less than 80 mmHg (SpO_2, <95%) with a target value of PaO_2 of 80 mmHg or SpO_2 of about 95%. Hypoxemia can also be involved in the contraction of the airway smooth muscle. Simultaneously, arrangements for endotracheal intubation and ventilator should be made.

(6) Inhaled anticholinergics

Anticholinergics (ipratropium or oxitropium), added to a β_2-agonist during acute exacerbations, may enhance the bronchodilator effect to improve symptoms and respiratory function[92] and reduce hospitalization rates.

(7) Other therapies

- Antibiotics are administered to patients with bacterial infection accompanied by fever and purulent sputum.
- Expectorants and mucolytic agents on sputum are not essential.
- Analgesics are not generally used.
- Antihistamines have no immediate effects on acute asthma symptoms.
- In fluid replacement, caution should be exercised

Table 20 Treatment steps for asthma exacerbation

	Treatment	Home remedy, emergency visit and hospitalization, and ICU treatment †
Treatment step 1	Inhaled β_2-agonist, as needed ‡ Theophylline agent, as needed	Home remedy
Treatment step 2	Repeated inhalation of β_2-agonist using a nebulizer § Intravenous drip infusion of aminophylline ¶ Intravenous drip infusion of steroid ‖ Oxygen (1-2 L/min with nasal cannula) Subcutaneous injection of Bosmin® (adrenaline, 0.1%)# Consider anticholinergic inhalation.	Emergency visit - If symptoms improve within 1 h, the patient may be discharged. - Insufficient response within 2-4 h - No response within 1-2 h Hospital admission: Switch to treatment step 3 as severe exacerbation.
Treatment step 3	Continuous drip infusion of aminophylline †† Repeated intravenous drip infusion of steroid ‖ Oxygen (Target PaO_2 is about 80 mmHg) Subcutaneous injection of Bosmin® (adrenaline, 0.1%)# Repeated inhalation of β_2-agonist using a nebulizer §	Emergency visit If no response within 1 h, hospitalization. If exacerbated, switch to treatment for serious exacerbation.
Treatment step 4	Continue the above treatment. If symptoms and respiratory function are exacerbated, conduct intubation. † Despite oxygen inhalation, ≤50 mmHg PaO_2 and/or rapidly elevated $PaCO_2$ with impaired consciousness. Mechanical ventilation †, Bronchial lavage Consider general anesthesia (using isoflurane, sevoflurane, etc.).	Immediate hospitalization and ICU treatment †

Aim of treatment: Elimination of dyspnea, normal movement, normal sleep, and normal everyday life. PEF rate is ≥80% of the predicted value or the best value. Oxygen saturation >95% (values after bronchodilator administration). No exacerbation of asthma symptoms by routine medication and inhalation.

Consider treatment step-up when the aim of treatment cannot be achieved within 1 hour.

† ICU or hospital rooms where tracheal intubation, assisted ventilation, bronchial lavage, etc., can be performed and continuous monitoring can be conducted using a sphygmomanometer, electrocardiogram, and pulse oximeter. Since intubation and mechanical ventilation during severe respiratory insufficiency are often threatening to life, they should be used by experienced specialists when inevitable in emergency.

‡ Repeat 1-2 puffs of β_2-agonist pMDI twice at an interval of 20 min. If ineffective or exacerbated, use 1 tablet of β_2-agonist or 200 mg of aminophylline.

§ Inhalation of β_2-agonist using a nebulizer: repeat every 20-30 min. Monitor the pulse to be maintained at ≤130/min.

¶ Intravenous drip infusion of aminophylline (6 mg/kg) in 200-250 mL of isotonic fluid: Administer the first half for about 15 min and the remaining half for about 45 min. If toxic symptoms (headache, nausea, palpitation, extrasystole, etc.) occur, discontinue the infusion. When a sufficient amount of theophylline was administered before exacerbation, reduce the dose of aminophylline to half or less. Routinely, measure serum theophylline levels in patients receiving it, wherever possible.

‖ Intravenous drip infusion of steroids: intravenous drip infusion of 200-500 mg of hydrocortisone, 40-125 mg of methylprednisolone, or 4-8 mg of dexamethasone or betamethasone. Subsequently, conduct intravenous drip infusion of 100-200 mg of hydrocortisone, or 40-80 mg of methylprednisolone every 4-6 h as needed, or 4-8 mg of dexamethasone or betamethasone every 6 h as needed, or oral prednisolone (0.5 mg/kg/day). Steroid succinate esters (i.e., methyl prednisolone, prednisolone sodium succinate) should be avoided in patients who have or are suspected of having aspirin-induced asthma.

Bosmin® (adrenaline, 0.1%): Bosmin® (0.1-0.3 mL) can be repeatedly administered at intervals of 20-30 min. Monitor the pulse to be maintained at ≤130/min. This agent is contraindicated in patients with ischemic heart disease, glaucoma (except for open-angle [simple] glaucoma), and hyperthyroidism. Sphygmomanometry and electrocardiography are required for patients with hypertension.

†† Continuous intravenous infusion of aminophylline: following the first intravenous infusion (see # above), conduct continuous intravenous infusion of 250 mg of aminophylline (1 tube) for 5-7 h (about 0.6-0.8 mg/kg/h). Monitor serum theophylline levels to be maintained at 10-20 μg/mL (15-20 μg/mL to achieve the maximum effects). If toxic symptoms occur, discontinue the infusion.

Table 21 Severity of an asthma attack and the corresponding treatment step

Exacerbation intensity‡	Dyspnea	Movement	Laboratory data†				Treatment steps in exacerbation
			PEF	SpO_2	PaO_2	$PaCO_2$	
Wheezing/ chest tightness	Dyspnea when in a hurry Dyspnea when in moving	Almost normal	≥80%	≥96%	Normal	<45 mmHg	Treatment step 1
Mild (mild exacerbation)	Dyspnea but no trouble with lying down	Slight dyspnea					
Moderate (moderate exacerbation)	Dyspnea with trouble with lying down	Difficulty in moving Difficulty in walking	60-80%	91-95%	>60 mmHg	<45 mmHg	Treatment step 2
Severe (severe exacerbation)	Dyspnea, cannot move	Abasia Difficulty in speaking	<60%	≤90%	≤60 mmHg	≥45 mmHg	Treatment step 3
Serious	Respiratory attenuation Cyanosis Respiratory arrest	Anepia Akinesia Confusion Impaired consciousness Incontinence	Immeasurable	≤90%	≤60 mmHg	≥45 mmHg	Treatment step 4

† Refer to values after bronchodilator administration.

‡ Determine exacerbation grade based on the severity of dyspnea, referring to other items. If symptoms of different exacerbation intensities coexist, use more severe one.

for dehydration, although substantial fluid replacement is generally unnecessary.

4.2.2. Management at home

Since the severity of asthma symptoms vary widely from mild wheezing/chest tightness to severe attacks showing abasia and speech difficulty, management of acute exacerbations must be tailored according to their severity, and patients must be informed about the individualized approach. For this purpose, oral explanation alone is not sufficient, and the patient should be provided with a self-management plan (action plan) with specific instructions for each condition.[93] To treat wheezing/chest tightness and moderate asthma symptoms, 1 to 2 puffs of a SABA should be administered using a pMDI. If the effects are insufficient, inhalation should be repeated every 20 min for 1 h and subsequently once an hour. At this time, an oral β_2-agonist or theophylline drug (aminophylline) can be used at the same time.

Patients can be treated at home continuously when these agents eliminate symptoms (≥80% of the predicted PEF rate or the best value) and their effect continues for 3 to 4 h. However, if no therapeutic effect can be achieved, an oral corticosteroid (about 15-30 mg of prednisolone) should be administered, and the patient should refer to an emergency outpatient unit immediately.

4.2.3. Treatment procedures in emergency outpatients (Table 20)

Immediately on arrival, the severity of an asthma attack should be determined. Asthma attack is roughly classified according to the severity of symptoms as follows: (i) mild: dyspnea but no difficulty in lying down; (ii) moderate: difficulty in lying down and walking; (iii) severe: difficulty in moving, abasia, and speech difficulty; and (iv) serious symptoms: cyanosis, impaired consciousness, and respiratory arrest. Treatment is classified into four treatment steps for asthma exacerbations (Table 20). It is also important to examine the history quickly and efficiently by checking the points listed below; however, the initiation of treatment should not be delayed.

- Time of onset and cause of exacerbations.
- Extent of exercise limitation and sleep disturbance.
- History of recent drug administration, names of drugs and time of their last administration, and use of steroids.
- Hospitalization and emergency visit due to asthma.
- History of respiratory failure and intubation due to asthma.
- Cardiopulmonary diseases and complications.
- History of AIA and drug allergies.

After assessment of the severity of an asthma attack, the treatment step is selected (Table 21).

(1) Wheezing/chest tightness, mild symptoms (Mild exacerbations)

a) Assessment

Wheezing and chest tightness are felt during breathing, but almost normal movements are maintained. The term "mild symptoms" indicates mild dyspnea at rest, such that allows the patient to lie down but causes mild difficulty with movement. These symptoms do not affect daily activities. The reference value of the PEF rate is 80% and higher of the predicted value or the best value (after bronchodilator administration). A history of asthma and other diseases should be taken in new patients. All patients should be asked about treatments administered after onset and should undergo a physical examination such as chest auscultation. Patients with dyspnea possibly unrelated to asthma should be examined by radiography and electrocardiogram.

b) Treatment

Administer step 1 treatment for asthma exacerbations. Inhale a β_2-agonist using a pMDI, DPI, or nebulizer.

If symptoms disappear and conditions are stable for 60 min without additional treatment, ensure that there is no airway obstruction (≥80% %PEF) and discharge the patient. If symptoms are not improved and airway obstruction continues (≤80% %PEF), introduce step 2 treatment.

(2) Moderate symptoms and continuous mild symptoms (moderate exacerbation)

a) Assessment

Moderate asthma symptoms (i.e., dyspnea and orthopnea at rest, difficulty with movements). The PEF rate is in the range of 60% to 80% of the predicted value or the best value. When the patient is known to have asthma, he or she should be examined for exacerbation as usual. The entire lungs should be examined for continuous rales and the presence of cyanosis. For a differential diagnosis of other diseases, various examinations such as chest radiography, electrocardiogram, blood count, and arterial blood gas analysis should be performed.

b) Treatment

Administer step 2 treatment for asthma exacerbations.

(i) Administer an inhaled β_2-agonist, 0.3 to 0.5 mL, diluted in an appropriate volume of physiological saline, using a nebulizer: repeat the inhalation every 20 to 30 min. The pulse should be maintained at a rate of 130/min and lower. The use of a pMDI has the same effects. If symptoms improve within 20 to 60 min and are stable for 60 min after the last administration (% PEF is ≥80%) and SpO_2 is lower than 95%, the patient may be discharged. If symptoms do not improve (% PEF is ≤80%), the following treatments should be initiated.

(ii) Intravenous infusion of aminophylline (250 mg/ampule) 6 mg/kg in 200 to 250 mL of isotonic fluid: administer the first half for about 15 min and the remaining half for about 45 min. If a sufficient amount of theophylline had been administered before exacerbations, reduce the dose of aminophylline to half or less. If toxic symptoms of theophylline (headache, nausea, vomiting, tachycardia, arrhythmia, and others) occur during infusion, immediately discontinue the administration. Monitor serum theophylline levels during treatment wherever possible.

(iii) Intravenous drip infusion of 200 to 500 mg of hydrocortisone, 40 to 125 mg of methylprednisolone, or 4 to 8 mg of dexamethasone or betamethasone: systemic steroid administration should be initiated immediately in patients with moderate or more severe exacerbations, or patients who respond poorly to the initial treatment with an inhaled β_2-agonist. Steroid administration should also be initiated immediately in patients who receive a high dose of an ICS (equivalent to FP ≥800 μg/day) or receive an oral corticosteroid on regular basis, or who belong to a high-risk group[94] (Table 19). Steroid phosphate esters (i.e., dexamethasone or betamethasone) should be used in patients who have or are suspected of AIA. Furthermore, about an hour of intravenous infusion is recommended in patients with unconfirmed AIA, or in patients who have received the agent for the first time.

(iv) Oxygen: nasally administer oxygen at a dose of 1 to 2 L/min to patients with severe dyspnea (PaO_2, ≤ 80 mmHg).

(v) Subcutaneous injection of 0.1 to 0.3 mL of adrenaline (0.1%): adrenaline can be repeatedly administered at intervals of 20 to 30 min as needed, but the pulse should be monitored and generally kept below 130/min. Adrenaline should be administered carefully if dehydration and metabolic acidosis are present. In addition, caution should be exercised for agents such as halothane, antipsychotic, α blocker, and catecholamine, the concomitant use of which is contraindicated. Adrenaline is generally contraindicated in patients with complications, such as arteriosclerosis, hyperthyroidism, glaucoma (except for open-angle [simple] glaucoma), diabetes mellitus, serious arrhythmia, and psychoneurosis, but if must be used, it should be administered with care. The use of adrenaline is preferably avoided in pregnant women. Hypoxemic patients are at high risk for adverse effects.

(vi) Inhaled anticholinergics: anticholinergics can be administered additionally to β_2-agonist because of their additive effect.

c) Action plan after treatment

(i) Favorable response: when wheezing and dyspnea are absent for 1 h (%PEF, ≥80%; SpO_2, >95%), discharge the patient and step up the long-term treatment. Subsequently, apply medications for long-term management according to an appropriate treatment

Table 22 Conditions requiring tracheal intubation

- Severe ventilatory impairment or cardiac or respiratory arrest
- Marked respiratory muscle fatigue
- <50 mmHg PaO_2 even after maximum oxygenation
- ≥5 mmHg/h elevation in $PaCO_2$
- Marked elevation in $PaCO_2$ and consciousness disorder

step of asthma. In patients receiving an oral steroid, consider adding or increasing the dose of corticosteroid for 1 to 2 weeks.

(ii) Insufficient response: mild wheezing and continued dyspnea (<80% %PEF, ≤95% SpO_2). Step up to step 3 treatment (see the next chapter), but if symptoms do not improve within 2 to 4 h, consider hospitalization.

(iii) No response: marked extensive wheezing and dyspnea (orthopnea) (%PEF, ≤70%) persist. Step up to step 3 treatment, but if symptoms do not improve within 1 to 2 h after addition of intravenous steroids, consider hospitalization.

(iv) After hospitalization: continue step 3 treatment both in the case of b) and c).

(3) Severe symptoms (severe exacerbations) or continued moderate symptoms

a) Assessment

If the patient with asthma symptoms presents at an emergency department, briefly check the physical findings to determine the severity and differentiate the findings from other diseases that cause dyspnea. Subsequently, ask short relevant questions about the causes of exacerbation and previous treatment.

(i) Symptoms and physical findings: patients with serious symptoms adopt a hunched position and cannot move because of dyspnea. They may suffer from speech difficulty, confusion, or unconsciousness. Accessory respiratory muscles are used for breathing, with the suprasternal space depressed. Usually, marked wheezing is heard in the chest. Attenuation or elimination of breath sounds indicates respiratory arrest or its signs, but cyanosis is usually absent.

(ii) Tests: generally, spirometry cannot be performed. If possible, the PEF is less than 60% of the predicted value or the best value. Blood gas analysis is more reliable to determine severity. Severe airway obstruction is indicated at SpO_2 of 90% and lower, and $PaCO_2$ in the range of 45 mmHg to 60 mmHg. Dyspnea due to other causes is differentiated from asthma using blood count, chest radiography, electrocardiogram, and other tests.

b) Treatment

Initiate step 2 treatment, followed by step 3 as continuous treatment.

(i) Initial treatment: in patients with serious symptoms, who cannot move and have speech difficulty, establish venous access immediately, initiate treatment with an inhaled β_2-agonist using a nebulizer, and administer adrenaline (0.1%), aminophylline, and steroids according to step 2 treatment.

- Administer from 0.3 to 0.5 mL of an inhaled β_2-agonist, diluted in physiological saline, using a nebulizer.
- Intravenous drip infusion of aminophylline (250 mg/ampule) 6 mg/kg in 200 to 250 mL of isotonic fluid. Administer the first half for about 15 min and the remaining half for about 45 min. When a sufficient amount of theophylline had been administered before exacerbations, reduce the dose of aminophylline to half or less.
- Intravenous drip infusion of 200 to 500 mg of hydrocortisone or 40 to 125 mg of methylprednisolone or 4 to 8 mg of dexamethasone or betamethasone. Steroid phosphate esters (i.e., dexamethasone or betamethasone) should be used in patients who have or are suspected of having AIA. In addition, intravenous drip infusion spending for about one hour is recommended for patients, in whom the presence or absence of AIA is unknown, or who receive the agent for the first time.
- Subcutaneous injection of 0.1 to 0.3 mL of adrenaline (0.1%). Subcutaneous injection of adrenaline (0.1%) can be repeated at intervals of 20 to 30 min as needed. The pulse should be monitored and generally kept below 130/min. The patient should be carefully monitored for the presence of the above contraindications.
- Oxygen. Target PaO_2 in oxygenation is around 80 mmHg. Caution should be exercised for CO_2 narcosis in patients complicated by COPD. In poorly responsive patients, check that consciousness is normal and introduce noninvasive positive pressure ventilation (NPPV), intubation, mechanical ventilation, and others, immediately depending on the patient's status. NPPV improves the patient's breathing pattern through pressure support ventilation and avoidance of airway collapse at the end-expiration phase by positive end-expiratory pressure (PEEP), and thus may be effective in terminating the vicious circle during acute asthma attack.[95] Consider hospitalization (immediately hospitalize patients if no improvement is noted within 1 h after treatment).

(ii) Continuous treatment: continue step 3 treatment.

- Continuous intravenous drip infusion of aminophylline at a dose of 0.6 to 0.8 mg/kg/h. Target serum level of aminophylline is 8 to 20 μg/mL. If symptoms that suggest intoxication develop, immediately slow down or discontinue the administration to examine overdose by measuring the theophylline level. Consider various factors affecting the serum theophylline level (Table 18).
- Intravenous drip infusion of 100 to 200 mg of hy-

Table 23 Conditions requiring hospitalization

- Moderate symptoms (60-80% %PEF), insufficiently responsive to 2- to 4-h treatment (≤70% %PEF) or nonresponsive to 1- to 2-h treatment
- Severe symptoms (<60% %PEF) nonresponsive to treatment within 1 h
- History of severe asthma attack requiring hospitalization
- Chronic symptoms that had continued for a long period (several days to 1 week) until emergency visit
- Complications, such as pneumonia, atelectasis, and pneumothorax
- Mental disorders or communication difficulties
- Difficulties in consulting a medical institution, e.g., heavy traffic when returning home

Table 24 Conditions for admission to ICU

- No response to initial treatment in an emergency room
- Symptoms suggesting risks of confusion, respiratory arrest, and unconsciousness
- Imminent respiratory arrest: ≥45 mmHg $PaCO_2$ continues (however, respiratory insufficiency may occur regardless of $PaCO_2$ level)

drocortisone or 40 to 80 mg of methylprednisolone every 4 to 6 h as needed. Alternatively, intravenous infusion of 4 to 8 mg of dexamethasone or betamethasone every 6 h as needed. Alternatively, oral prednisolone (0.5 mg/kg, 20-30 mg/day). Additional intravenous drip infusion of 100 to 200 mg of hydrocortisone, or 40 to 80 mg of methylprednisolone every 4 to 6 h as needed, or 4 to 8 mg of dexamethasone or betamethasone every 6 h as needed. Steroid phosphate esters (i.e., dexamethasone or betamethasone) should be selected in patients who have or are suspected of having AIA. In addition, spending about an hour for the intravenous drip infusion is recommended when the presence of AIA is not confirmed, or the steroid has been administered for the first time. Since hydrocortisone causes edema when administered for 3 days or longer, switch to a different steroid if steroid administration has to be continued after 3 days. As an oral drug, administer an oral prednisolone (approximately 0.5 mg/kg, 20-30 mg/day) once in the morning, and, after remission, discontinue the administration within 7 to 14 days or reduce it to the usual dose before attacks. There is no benefit from tapering the dose of an oral corticosteroid after remission, and the administration may be discontinued abruptly.[96] Initiate the administration of an ICS when inhalation becomes possible during the course of treatment.

- Oxygen. Continuously administer an optimal dose.

(4) Serious asthma symptoms and emergency (serious exacerbations)

a) Assessment

Emergency care is indicated (e.g., endotracheal intubation and mechanical ventilation), when clinically severe ventilatory impairment or respiratory arrest occurs, when there is no response to the above treatments, when PaO_2 is less than 50 mmHg even after maximum oxygenation and/or rapid increase of $PaCO_2$ with impaired consciousness occurs, or when $PaCO_2$ has been rapidly increasing to ≥5 mmHg and higher an hour. If $PaCO_2$ exceeds 45 mmHg, prepare intubation for mechanical ventilation. The cases that require endotracheal intubation are presented in Table 22. Since intubation is associated with a considerable risk, an experienced specialist should be consulted wherever possible. NPPV may improve the patient's breathing pattern through pressure support ventilation and prevent airway collapse at the end-expiration phase by PEEP (treatment by an experienced specialist is desirable). Note that initiation of intubation or mechanical ventilation is not delayed, especially in the case of disturbed consciousness or hypersecretion.

b) Treatment

Administer step 4 treatment.

(i) Endotracheal intubation and artificial respiratory management[97]: conduct endotracheal intubation according to the routine procedure. Immediately connect the endotracheal tube to a volume-cycled ventilator. Adjust the ventilator with 100% fraction of inspired oxygen (F_IO_2), 5 to 8 mL/kg tidal volume. Set the ratio of inspiratory-to-expiratory phases at 1 : 3 or above and equalize the duration of each phase. Keep the airway pressure below 50 cm H_2O (maximum) and from 21 to 25 cm H_2O (average). Subsequently, set F_IO_2 at about 80 mmHg PaO_2. Here, ensure the maintenance of PaO_2 and the prevention of barotrauma even if $PaCO_2$ values are high, until exacerbations improve. In severe exacerbations, the airway pressure at the end of expiration is often elevated and airway is under the auto-PEEP condition. As auto-PEEP is often caused by central airway obstruction, it is reported that PEEP by mechanical ventilation may be effective to cancel the auto-PEEP. However, in principle, avoid using a ventilator at high PEEP, considering the risk of barotrauma. Intubation should preferably be as short as possible.

(ii) Treatment for exacerbation: immediately after intubation, 0.3 to 1.0 mL of a β_2-agonist or adrenaline (0.1% before dilution), both diluted 10-fold in physiological saline can be administered through an en-

Table 25 Conditions for allowing a patient to go home from an emergency room

- Identify and avoid the causes of exacerbation.
- Consult a physician as soon as possible after going home. Inform that continuous outpatient treatment is required until PEF returns to around the best value. In addition, examine the appropriateness of daily long-term treatment.
- Prescribe agents for 3-5 days when the patient goes home. Optionally, oral corticosteroids, as well as bronchodilators, are often needed.
- Check whether a patient has no trouble inhaling an inhalant or using a PEF meter adequately.
- Check whether a patient or his/her family has any problem with measures against exacerbation. It is particularly important to explain medicines and self-management in detail, to recognize the signs of exacerbation, immediately initiate treatment, and visit a medical institution.

Table 26 Conditions for discharge

- No need of inhaling a bronchodilator at ≤4-h intervals
- No short breath in walking
- No wake-up due to exacerbation at night or in the early morning
- (Almost) No abnormal physical findings
- PEF or FEV1 is ≥80% of predicted values. Diurnal variation is <20%.
- Normal PaO_2 value
- No trouble handling an inhaler. No trouble handling a spacer
- Appropriate actions against exacerbation.
- Patients understand conditions for discharge and prescription.
- Creation of a treatment plan after discharge

dotracheal tube. Initiate and continue systemic pharmacotherapy in the same manner as for severe asthma symptoms. For symptoms refractory to pharmacotherapy, general anesthesia using a narcotic agent (isoflurane, sevoflurane, and others) with a bronchodilator action is effective in airway relaxation.

Of note, the use of halothane should be avoided because it may cause ventricular arrhythmia when used simultaneously with β_2-agonists or aminophylline.

(iii) Conditions for discontinuation: extubate the patient when consciousness is restored and maximum airway pressure is reduced to 20 cm H_2O or below by spontaneous respiration without assisted respiration.

4.2.4. Indications for hospitalization

Consider hospitalizing a patient with symptoms that are not improved within several hours after the initiation of treatment (Table 23). Immediately hospitalize a patient with serious symptoms to conduct a more potent treatment.

4.2.5. Indications for intensive care unit admission

Consider asthma treatment in an intensive care unit or consult a specialist experienced in asthma treatment in the situations presented in Table 24.

4.2.6. Indications for discharge from an emergency room

Airway obstruction remits and PEF recovers to 80% and higher of the predicted value or the best value. The patient may be discharged if symptoms are stable for 60 min or longer after the last use of a bronchodilator. Conditions that must be met to discharge a patient from an emergency room are shown in Table 25.

4.2.7. Indications for discharge from the hospital

It is important to educate patients who experienced severe exacerbations requiring hospitalization about the high risk of death from asthma and to provide consistent instructions after discharge. Patients with repeated exacerbations should receive adequate treatment that considers psychological and social factors. It is necessary to check that symptoms have not exacerbated for 12 or 24 h or longer after treatment before discharge from the hospital (Table 26).

5. Indications for a Referral to a Specialist

Asthma is a complex disease caused by various external and physical factors. When the diagnosis or long-term treatment is challenging, the patient should be referred to a specialist based on cooperation system between hospitals and clinics.

6. Specific Considerations

6.1. Aspirin-Induced Asthma

6.1.1. Definition

AIA is not induced via IgE antibodies, so AIA is not allergic reaction against aspirin. NSAIDs, especially arachidonate cyclooxygenase-1 (COX-1) inhibitors, such as aspirin, induce strong symptoms in the airways, including nasal congestion, nasal discharge, and asthma attack. As the inhibitory effects of NSAIDs on the COX activity are much higher, asthmatic reaction appears to be stronger. Because COX-2 inhibitors such as cerecoxib can be used safely in patients with AIA, this reaction is due to the inhibition of COX-1. AIA is also known as "aspirin-intolerant asthma"; however, recently, it has been termed "aspirin-exacerbated respiratory disease" because it also induces symptoms in the upper respiratory tract.[98]

6.1.2. Epidemiology, clinical aspect, and symptoms

About 5% to 10% of the patients with adult asthma have AIA, and the ratio of men to women is 1 : 2. AIA usually develops in 20- to 40-year-old individuals, and is characterized by weak or no atopy.[99] Half of these individuals are severe asthmatics and often have fixed airflow obstruction. When the attack in AIA is caused by the administration of COX inhibitors, watery rhinorrhea and nasal congestion often develop as prodromal symptoms that may be accompanied by facial flushing, conjunctival hyperemia, and digestive symptoms (abdominal pain, diarrhea, and others). Sometimes, chest pain, itching, and urticarial may occur simultaneously. Patients with AIA often have eosinophilic rhinitis with a nasal polyp and distorted sense of smell. Similarly, more than half of asthmatic patients with a nasal polyp have AIA. Nasal symptoms, especially distorted sense of smell, are observed several years prior to the onset of asthma symptoms. More than 50% of the patients have eosinophilic otitis media, about 30% have symptoms of eosinophilic colitis, and about 10% to 20% have variant angina pectoris.

6.1.3. Pathogenesis

The pathogenesis of AIA is thought to be the overproduction of CysLTs.[100] Urinary LTE_4 concentrations is several times higher in stable patients with AIA compared with individuals without AIA, and when AIA attack occurs, LTE_4 levels are more than several times higher compared with the stable condition.

6.1.4. Diagnosis

Because of its nonallergic mechanisms, AIA cannot be diagnosed with general tests for allergies. To diagnose AIA, a medical interview and challenge test are required. In a medical interview, a physician should ask about the side effects of NSAIDs, disturbances in the sense of smell, and the presence of a nasal polyp and sinusitis. In addition, AIA can be diagnosed if asthmatic patients fulfill more than two of the following criteria: moderate-to-severe asthma, asthma onset after early adolescence, weak or no atopy, symptoms of refractory cough, or eosinophil count in the peripheral blood exceeding 10%. To confirm the diagnosis, it is recommended to perform a challenge test for NSAIDs, preferably in a specialist center with experienced experts.

6.1.5. Management of fever and pain in patients with AIA

Oral acetaminophen is considered to be safe compared with regular NSAIDs. It has been reported that in 34% of asthmatic patients the pulmonary function worsens at a dose of 1000 to 1500 mg of acetaminophen; therefore, it is safe to administer less than 500 mg of acetaminophen (or preferably even less than 300 mg) in patients with AIA.[101] A selective COX-2 inhibitor, cerecoxib, has a high safety profile but it rarely induces an asthma attack in unstable patients with severe asthma.

6.1.6. Management of aspirin-induced attack of asthma

The management of an asthma attack induced by NSAIDs is basically similar to the ordinary treatment for exacerbations, but the following three issues should also be taken into consideration.

(1) Succinic esters of steroids often induce a severe asthma attack (sometimes fatal) if administered rapidly. In patients with severe asthma, the severity of an asthma attack is higher. A high dose of these agents, if administered rapidly, may induce a severe attack. Most of the patients with AIA are potentially hyperresponsive to succinic ester of steroids. Phosphate esters of steroids themselves do not affect AIA, but some additives could cause worsening of exacerbations. Therefore, a rapid intravenous administration of these agents is not safe, even in intramuscularly. A rapid intravenous administration of these agents is contraindicated, and they should be administered slowly for more than 1 to 2 hours.

(2) Inhalation of bromhexine hydrochloride salt is known to induce an aspirin-induced attack of asthma, while oral administration is known to be safe.

(3) Adrenaline (0.1%) is useful in the treatment of aspirin-induced attacks of asthma. A low dose of adrenaline (0.1-0.2 ml) should be used for AIA and repeated administration is possible.

6.1.7. Long-term management of aspirin-induced asthma, prevention of nonsteroid anti-inflammatory drug use, and desensitization of aspirin

Long-term management of AIA is basically similar to that of asthma without AIA. Because CysLTs are involved in the pathogenesis of AIA, LTRAs in combination with ICSs are a better choice for long-term management.[101] LTRAs can improve both the symptoms of asthma and nasal sinusitis and can significantly improve, although not completely, the reaction of AIA. Treatment for chronic sinusitis and nasal polyp is important to stabilize AIA. A severe nasal polyp should be removed by endoscopic surgery.

6.2. Exercise-Induced Asthma

6.2.1. Pathogenesis and mechanism of exercise-induced asthma

Asthma attack or transient bronchoconstriction several minutes after exercise is called "exercise-induced asthma" or exercise-induced bronchospasm. EIA is often induced by a relatively intensive exercise up to 80% of the maximum heart beats for 3 to 8 minutes.[102] Exercise-induced attack of asthma may be induced by occasional swimming, running (especially short- or

intermediate-distance splint), and inhalation of cold and dry air.

6.2.2. Prevention of exercise-induced asthma

Inhaled β2-stimulants are superior to other asthma drugs owing to their bronchodilatory action; they prevent bronchoconstriction induced by EIA. LTRAs are also useful and comparable or superior to LABAs for the prevention of EIA. EIA should be prevented by long-term management with controller drugs and inhalation of β2-stimulants before exercise.

6.2.3 Management of asthma in athletes

(1) Pathogenesis of asthma in athletes

The prevalence of asthma in athletes is higher than that in nonathletes. The pathogenesis of asthma in this group is associated not only with the general mechanisms including the cooling of airways or change of osmotic pressure, but also with some specific mechanism. Hard exercise associated with excessive ventilation of up to 200 L/min induces the stretching of the airway epithelial cells and causes tissue damage and repair in the airways,[103] resulting in airway hyperresponsiveness and remodeling.

(2) Diagnosis of asthma in athletes

When athletes participate in international or domestic athletic competitions, they should undergo an objective diagnose of asthma. If they are treated with asthma drugs that are prohibited owing to their doping effect, they have to present a medical certificate issued by a physician and apply for a Therapeutic Use Exemption (TUE).

(3) Treatment and management of asthma in athletes

Because a number of asthma drugs is prohibited by the World Anti-Doping Agency, a physician should be careful about the use of asthma drugs in athletes. An application for TUE is needed when the use of asthma drugs is required, and asthma should be diagnosed on the basis of objective findings. Although long-term management and treatment of asthma exacerbations in athletes is similar to those in general asthmatic patients, a number of asthma drugs is prohibited in athletes. Drugs that are permitted include ICSs, LTRAs, oral theophylline, salmeterol, and formoterol, while the list of prohibited drugs includes patch formulation of tulobuterol and all oral β2-stimulants. As concerns relievers, salbutamol is permitted at a dose of up to 1600 μg/day without the need to apply for TUE. When asthma is controlled by an inhalation of BUD plus formoterol, a maximum dose of 36 μg of formoterol daily (8 inhalations/day) is permitted. Systemic oral or intravenous corticosteroids need to be administered retroactively before scheduled athletic competition.

(4) Prevention of asthma in athletes

To prevent exercise-induced attack of asthma, athletes need to be treated with SABAs 10 to 15 min prior to exercise. If asthma symptoms are intense, an LTRA is administered in combination with ICSs as controllers. Airway hyperresponsiveness improves or resolves after athletes stop intensive training for a competition.

6.3. Elderly Patients with Asthma

According to the World Health Organization's definition of elderly persons, asthmatic patients older than 65 years may be defined as elderly. Because elderly adults vary considerably in senescent changes related to aging and have comorbidities, the pathophysiology of asthma in this patient group is more complicated compared with younger asthmatic patients. Sometimes, the diagnosis of asthma is difficult because of senescent changes. In 2012, 1874 patients were reported to die of asthma, of whom 90% were older than 65 years. To reduce mortality from asthma, it is important to prevent death as well as to properly diagnose and manage asthma in elderly patients.

6.3.1. Diagnosis

Asthma symptoms in elderly persons are similar to those in younger patients. However, in elderly patients with asthma in remission, the symptoms and pulmonary function are not as stable as in younger patients. Because elderly patients are insensitive to the sensation of dyspnea from bronchoconstriction, the degree of severity is sometimes underestimated. The diagnosis of asthma may be difficult in the case of a mild disease or the presence of comorbidities. Sometimes, it may be difficult to recognize the clinical picture of asthma because elderly patients often have COPD, heart failure, and reflux esophagitis. To diagnose asthma in an elderly person, lung cancer, and lung tuberculosis along with its sequelae have to be excluded. The measurement of brain natriuretic peptide is useful to distinguish asthma from heart failure. Chest radiograph and echocardiography are also useful in a differential diagnosis.

6.3.2. Treatment

When introducing treatment in elderly patients with asthma, complications such as COPD, effectiveness of asthma drugs, adherence to drug regimen, and approach to the use of inhaler should be considered. A physician should be careful about asthma exacerbations induced by NSAIDs used for arthritis and β-blockers used for hypertension and glaucoma.

(1) Chronic obstructive pulmonary disease

COPD is a significant coexisting disease that should be included in a differential diagnosis in elderly patients with asthma. The pathophysiological features

of asthma are eosinophil-predominant inflammation from the central to peripheral airway and reversible airway obstruction. On the other hand, in COPD, neutrophil-predominant inflammation and structural alterations, located in the peripheral airway and alveolar capillary vessels are observed. Moreover, in COPD, airway obstruction is caused by a combination of peripheral airway and emphysematous lesions. Thus, a differential diagnosis based on clinical symptoms is often difficult, although the diseases differ in their pathophysiological characteristics. According to some reports, 18.4% to 31.7% of elderly patients aged 65 years and over actually have both diseases. A previous epidemiological report showed that more than half of the elderly patients with obstructive pulmonary disease had asthma-COPD overlap syndrome (ACOS).[104] Because patients with overlap syndrome are reported to have a rapidly decline in the pulmonary function, an ICS or a combination of an ICS and inhaled LABA is recommended in the early stage of the disease, in addition to long-acting bronchodilators, which are mainly used in patients with COPD.[105] To treat airway obstruction in patients with overlap syndrome, LAMA and theophylline are used.

(2) Dementia

A physician should carefully evaluate adherence to the treatment regimen and technique of inhalation in patients with dementia. In such cases, health care personnel may be needed to support and instruct patients in the use of asthma drugs including inhaled agents.

(3) Cranial nerve disease; disease of motor organs

Health care personnel may be needed to support and instruct patients with cranial nerve disease and disease of motor organs in the use of asthma drugs.

6.3.3. Asthma drugs

(1) Corticosteroids

In elderly patients with asthma, oral corticosteroids may cause neurological symptoms including excitation or confusion. ICSs are the first-choice drugs because they do not cause systemic side effects even in elderly patients. It is important for elderly patients to repeatedly check their technique of inhalation and receive proper instruction on how to use inhaled drugs because various types of devices for inhaled drugs are developed. When elderly patients are unable to use a dry-powder inhaler, it is sometimes useful to change to a pMDI, use spacer of inhaled drugs or change to suspension of corticosteroids by jet nebulizer. Long-term treatment with high-doses of ICSs (equivalent dose of 800 μg of FP per day) may cause systemic side effects including progression of osteoporosis, glucose metabolism, change of estrogen levels, hypertension, peptic ulcer, or immunosuppression. Female elderly patients are particularly susceptible to progression of osteoporosis and bone fracture.

(2) Bronchodilators

Bronchodilators such as SABAs and LABAs with ICSs are used in elderly patients, but their effectiveness is lower than that in younger patients. The effectiveness and side effects of these drugs should be carefully evaluated in elderly patients. LAMAs are relatively useful in patients with coexisting COPD or in those who are less responsive to β_2-stimulants. A LAMA is used with other asthma drugs such as ICSs or in combination with ICSs and inhaled LABAs. A LAMA needs to be administered by paying thorough attention to its influence on glaucoma (eye ball pressure) and anuresis (difficulty in urination) by benign prostatic hypertrophy. Because the effectiveness of inhaled LABAs in chronic asthma exacerbations does not differ from that of oral asthma drugs, oral drugs are frequently used in elderly patients. Patch formulation of tulobuterol is also useful in this patient group. The side effects of β_2-stimulants affecting the cardiovascular tend to be more common in elderly than in younger patients. Because β_2-stimulants often cause tremor and tachycardia, a single-dose inhalation of β_2-stimulants is recommended in elderly patients with cardiovascular disease.

(3) Theophylline

Theophylline levels in the peripheral blood should be maintained at 5 to 10 μg/ml, and concomitant use with other asthma drugs is recommended. A physician should monitor blood theophylline levels because the side effects in the case of drug overdose may be severe and even fatal in elderly patients. Concomitant use of theophylline with other asthma drugs is expected to improve the pulmonary function and QOL.

(4) Leukotriene receptor antagonist

LTRAs are effective for asthma treatment in elderly patients and is associated with a low risk of side effects.

(5) Antiallergic drugs

Antiallergic drugs are not effective in elderly patients because most of these patients have nonatopic asthma. Patients should be monitored for side effects because antiallergic drugs have low clearance.

6.4. Asthma in Early Adolescence or Early Twenties

6.4.1. Characteristics

The characteristics of asthma in patients in early adolescence or early twenties are listed below.

- If asthma has not been successfully controlled until this age, it often continues into adulthood (adult asthma).

- Mortality from asthma increases in this period compared with childhood.
- Patients and their parents tend to be discharged rapidly.
- These patients may have a lower quality of life owing to physical and emotional distress that affects their relationships as well as educational and work opportunities.
- Adherence to treatment regimen is often worse.
- A higher rate of asthma is observed in patients of this age with anxiety disorder and depression.
- The rate of medical consultations is significantly lower.
- Asthma attack is affected by menses.
- There is a relatively high risk of air leak syndrome such as mediastinal pneumothorax and subcutaneous emphysema.
- Patients often have atopic asthma despite a decrease in IgE levels.

6.4.2. Lack of adequate asthma control

The reasons why asthma control is inadequate in this patient group are listed below.

- Worse adherence to treatment regimen.
- The rate of medical consultations is significantly lower.
- Insufficient recognition of alterations in the pathophysiology of asthma.
- Inappropriate transition from pediatric to internal medicine care.
- Transition to single life.

6.4.3. Treatment considerations

A physician should treat asthmatic patients in early adolescence or early twenties with the awareness that these patients are incapable of self-management. These patients require a treatment plan and education in the management of asthma, but also specific problems typical for this patient group as listed in sections 6.4.1. and 6.4.2. should be addressed. When a physician introduces the patient to the asthma treatment plan, it is sometimes preferable that the patient alone takes part in the plan rather than with the assistance of his or her parents. It may be useful for the teaching staff to become involved in the treatment plan to avoid exposure to allergens and prevent EIA. It is necessary to make sure that patients with unstable asthma adhere to the treatment regimen.

6.5. Pregnancy

6.5.1. Influence of bronchial asthma on pregnancy and birth

The number of pregnant women with asthma tends to increase. Because functional residual capacity in pregnant women decreases even in normal pregnancy, an asthma attack accompanied by airway obstruction tends to cause hypoxemia in the fetus, posing risks of miscarriage, increased prematurity, and brain disorders.[106] In fact, premature delivery, low birth weight, and malformation are more common among patients with asthma. However, appropriate management of asthma can efficiently reduce the risk of death of the mother and fetus. Asthma causes no severe exacerbations when well controlled before delivery. In addition, asthma symptoms and airway hyperresponsiveness improve in late gestation, especially at 37 to 40 weeks. After birth, asthma status and airway hypersensitivity will be almost the same as before pregnancy.[107]

6.5.2. Effect of antiasthmatic drugs on pregnancy and birth

There is little evidence of teratogenicity for most antiasthmatic drugs (Table 27). There have been no reports associating the cleft palate and systemic high-dose steroid administration in humans. Since steroids do not readily pass through the placenta, their serum levels in fetuses are much lower than those in mothers, thus reducing the risk of adrenal suppression. To gain control of severe asthma, which causes fetal hypoxia and harms the mother's health, do not hesitate to administer a systemic steroid, although too long administration should be avoided wherever possible. ICSs are highly safe for the mother and fetus. According to the FDA, all asthma drugs are categorized into five classes based on safety (where A is the safest and E is the least safe). BUD (dry powder) is safe and is ranked in category B. Other ICSs are categorized as class C. On the other hand, ICSs are not classified in the National Asthma Education Prevention Program, and they are all recommended as the first-choice drugs in patient requiring step 2 treatment, even during pregnancy and breast feeding. There are no reports on teratogenicity of either inhaled or oral β_2-agonist, tulobuterol, and it is considered safe during pregnancy. Since a patch-type β_2-agonist is still a new drug form, introduced to the market only in Japan and South Korea, there is no evidence of its safety when used during pregnancy. However, patches are regarded as safe, since oral and inhaled forms (not on the market now) of tulobuterol are considered safe. There have been no reports on the teratogenicity of either oral or intravenous theophylline, suggesting its usefulness in controlling asthma during pregnancy. Since degradative rate of theophylline in the infant is slow, caution should be exercised in administering it to infants during lactation. Of allergy drugs, DSCG is considered safe. Since there is not enough evidence for the safety of LTRAs in humans, they should be administered during pregnancy only when the advantages outweigh the disadvantages. There seems to be little teratogenicity for classic antihistamines and relatively early-generation antiallergic drugs (epinastine, emedastine, ketotifen, tazanolast, pemirolast, azelastine, tranilast, and others). However, they should be administered during pregnancy only when the advan-

Table 27 Agents that can be used for asthma during pregnancy and precautions for their use

Inhalants
1. Inhaled corticosteroid †
2. Inhaled β_2 agonist (including a combination inhaler with an inhaled corticosteroid) ‡
3. Disodium cromoglycate (DSCG)
4. Inhaled anticholinergic §
Oral medicine
1. Theophylline sustained-release preparation
2. Oral β_2 agonist
3. Oral corticosteroid ¶
4. Leukotriene receptor antagonist ‖
5. Antihistamine ‖
Injections
1. Steroid ¶
2. Aminophylline
3. Adrenaline (0.1%) #
Others
Patch-type β_2 agonist: Tulobuterol ††

† Safety of budesonide in humans has been demonstrated in great detail.

‡ There is less evidence of the safety of long-acting inhaled β_2 agonist (LABA) than those of short-acting inhaled β_2 agonist (SABA). However, these agents are almost comparable in their safety during pregnancy.

§ There is no evidence of safety as a long-term management agent used during pregnancy. Safety as a reliever agent has been demonstrated.

¶ Prednisolone and methylprednisolone do not appreciably pass through the placenta.

‖ Can be administered during pregnancy only when the advantages outweigh the disadvantages. Have few risks even if unknowingly administered during pregnancy.

Use the subcutaneous injection of adrenaline only when inevitable. Generally avoid injection to pregnant women.

†† Safe as an inhalant or oral medicine. More evidences are required.

tages outweigh the disadvantages.

6.5.3. Asthma treatment during pregnancy

Considering the risks of an asthma attack on fetuses and pregnant women, it is more beneficial to continue treating patients with asthma during pregnancy. Appropriate measures (agents, allergen avoidance, environmental management, smoking cessation and separation of smoking areas, rest of mind and body, and others) should be taken against exacerbating factors to prevent symptoms and maintain respiratory function. ICSs are recommended as first-line therapy for long-term management. If an ICS alone is not effective enough, add a LABA, sustained-release theophylline, patch-type β_2-agonist, and others. Consider LTRAs only when the advantages outweigh the disadvantages (Table 27).

Allergen-specific immunotherapy (hyposensitization) can be continued during pregnancy if initiated before pregnancy. However, do not initiate the therapy during pregnancy. Continue the administration of anti-IgE antibody only when the advantages outweigh the disadvantages, because of the lack of data on anti-IgE antibody during pregnancy.

To treat exacerbations, administer a SABA. If the effects are insufficient, use oral medicine or injection (steroids and intravenous infusion of aminophylline). Oxygen inhalation is recommended to prevent fetal hypoxemia. Complications, such as abortion and premature delivery, premature rupture of the membranes, albuminuria, and eclampsia, are more common among patients with asthma. Certain congenital disorders (malformation) are seen in 2% to 4% of normal pregnancies. These complications should be explained in detail before administration to obtain patient's consent. It is more important to avoid exacerbation factors such as allergens and stress than to introduce pharmacological treatment. In addition, smoking, including passive smoking, has more serious consequences for the mother and fetus than any other clinically used agents do. This must be explained to patients, their spouses, and people around them to understand the necessity of smoking cessation.[108]

6.6. Comorbidity

6.6.1. Allergic rhinitis

Allergic rhinitis is divided into two major types: per-

ennial allergic rhinitis and seasonal allergic rhinitis. In Japan, about 40% of people have allergic rhinitis, and the number of patients with seasonal allergic rhinitis has increased recently. Allergic rhinitis is "type I allergic reaction disease in nasal mucosa and is characterized by 3 main symptoms including episodic and repeated sneezing, watery nasal discharge and nasal congestion". Asthma is commonly associated with allergic rhinitis. The lower respiratory tract is connected to the bronchus and the upper respiratory tract including the nose and paranasal sinuses, thereby influencing one another. Thus, a concept of "one airway, one disease" has been proposed. It has been reported that about 80% of asthmatic patients have allergic rhinitis, and 10% to 20% of the patients with allergic rhinitis also have bronchial asthma. A nationwide Japanese study has revealed that 67.3% of 26,680 asthmatics have allergic rhinitis.[109] Perennial allergic rhinitis caused by house dust mite is thought to be involved in the symptoms of asthma. Meanwhile, it has been reported that patients with seasonal allergic rhinitis experience asthma exacerbations during pollen allergy season.[110] In asthmatic patients with allergic rhinitis receiving nasal corticosteroids, asthmatic symptoms are often improved. LTRA is beneficial to allergic rhinitis as well as asthma. Allergen immunotherapy (hyposensitization therapy) is effective and can be used as the first-line treatment for allergic rhinitis. Even if patients are not completely cured, about 70% of them can reduce the dose of drugs for allergic rhinitis. Allergen immunotherapy is reportedly effective not only for allergic rhinitis but also for asthma control; however, the therapy should not be used in severe asthma.[111] It rarely causes an asthma attack (1/1,000-2,000 injections) and, even more rarely, a severe anaphylactic reaction (1/2,500,000 injection). After a subcutaneous injection, patients should be observed at least for 30 min. Long-term subcutaneous allergen immunotherapy (over 2 years) is required to bring effects. However, in some patients, the therapy has no effects on rhinitis. Sublingual allergen immunotherapy is also effective and less invasive.

6.6.2. Sinusitis; otitis media

(1) Chronic sinusitis

The association of asthma with chronic sinusitis is well-established. From 50% to 75% of asthmatic patients show abnormal findings in the paranasal sinuses on radiography. Chronic sinusitis is significantly more common in patients with severe asthma compared with those with mild asthma. The sinusitis score assessed by computed tomography is worse in asthmatics than in healthy subjects, and the score is positively correlated with the rate of asthmatic complications. Complication rate of nasal polyp is also higher in patients with more severe asthma. About 90% of the patients with AIA have nasal polyp. Low-dose macrolide therapy is effective for neutrophilic sinusitis and often improves asthma symptoms.

(2) Eosinophilic sinusitis; eosinophilic otitis media

Eosinophilic sinusitis is characterized by severe infiltration of eosinophils into the nasal mucosa and polyp, and is resistant to surgical treatment and macrolide therapy. Ethmoidal sinus is the main pathological lesion and is complicated with the disturbances in the sense of smell. Eosinophilic sinusitis is characterized by numerous polyps and severe eosinophilic infiltration. It usually develops in adulthoods and is considerably complicated with asthma. Eosinophilic sinusitis sometimes induces otitis media, called eosinophilic otitis media. Both diseases worsen the QOL by impairing the sense of smell and hearing. Only steroid treatment is effective in both diseases.

6.6.3. Churg-Strauss Syndrome (Eosinophilic granulomatosis with polyangiitis)

(1) Definition

CSS is characterized by a history of asthma, increase of eosinophil count in the blood and tissues, and multiple mononeuropathy and polyangiitis of many organs. CSS was previously known as "allergic granulomatous angiitis", but is now usually referred to as "eosinophilic granulomatosis with polyangiitis". CSS is one of antineutrophil cytoplasmic antibody (ANCA)-related systemic polyangiitis as well as granulomatosis with polyangiitis (Wegener's granulomatosis) and microscopic polyangiitis. The main pathological lesions in these diseases are observed in the microvessels of the arteriole and venula. Microvessels of the lungs and kidneys are often impaired. CSS is pathologically characterized by granulomatous necrotic polyangiitis infiltrated with eosinophils and lymphocytes.

The mechanisms underlying the onset of CSS remain unknown.

(2) Epidemiology

The onset of CSS is generally observed in patients older than 45 years. According to some Japanese reports, the prevalence of CSS is about 0.2% in male and 0.5% in female patients with asthma.

(3) Typical disease progression

Disease progression in CSS is divided into three clinical stages. In the first stage, patients develop eosinophilic sinusitis with asthma and nasal polyp. In the second stage, an increase in blood eosinophil count, worsening of asthma control, and occasionally, eosinophilic pneumonia are observed. In the third stage, systemic polyangiitis develops. In general, systemic polyangiitis occurs within several years after the onset of asthma. Typical symptoms of CSS are fever, muscle pain, and body weight loss. More than

90% of the patients have multiple mononeuropathy and eosinophilia in the peripheral blood. Skin symptoms, cardiac disturbance, and ischemic bowel disease are observed in 50% of the patients. Eosinophilia and elevated C-reactive protein, lactate dehydrogenase, and creatinine kinase levels are observed. Two-third of the patients have elevated serum IgE levels, positive conversion of rheumatoid factor, and increased platelet count. A positive ratio of MPO to ANCAs is about 30% to 40% in patients with CSS.

(4) Atypical disease progression

Most patients with CSS show typical disease progression. However, less symptomatic patients or those with fulminant progression of the disease are also reported.

(5) Characteristic manifestations in asthma with CSS

Asthma that precedes CSS usually develops in adulthood, and most of the patients with CSS have severe disease with marked eosinophilia. Less than a half of the patients are atopic before the onset of CSS. Although patients with CSS usually have severe asthma, airway hyperresponsiveness is mild before the onset of CSS. When in remission after the development of CSS, patients have fixed airflow limitation. It has been reported that eosinophil count both in the peripheral blood and sputum may predict relapse in CSS.[112] A pathological lesion of the upper airway is similar to that in AIA, and about 70% to 80% of the patients with CSS show eosinophilic sinusitis and, occasionally, eosinophilic otitis media.

(6) Diagnosis and treatment

A physician should carefully observe the clinical course of severe asthma, especially in patients with weak atopic eosinophilia, frequent eosinophilic pneumonia, or eosinophilic sinusitis. If patients have palsy, muscle weakness or symptoms, the differential diagnosis of CSS should be made. In case of atypical CSS, a pathological examination is required. The positive rate of perinuclear antineutrophil cytoplasmic antibody (P-ANCA) is about 30% to 40% for the diagnosis of CSS; therefore, CSS cannot be excluded on the basis of negative P-ANCA test results. Early diagnosis and treatment are important because polyangiitis may progress rapidly. Treatment for CSS after a clinical diagnosis should be started without a pathological examination. It is important to record any digestive disorders and cardiac diseases because they determine prognosis. The treatment of CSS essentially involves systemic steroids. In patients with severe disease, those with cardiac disease, or steroid-resistant patients, cyclophosphamide is concomitantly used with systemic steroids. High dose immunoglobulin is intravenously administered in treatment-resistant patients with nerve or cardiac disorders.

6.6.4. Allergic bronchopulmonary mycosis

(1) Definition

Because fungus repeatedly infects the airways of the sensitized asthmatic patients with specific IgE against the antigen of fungus in ABPM, not only IgE but also specific IgG is produced. Consequently, both type I and III allergic reactions occur in the airways and result in the destruction of the airway walls. Central bronchiectasis and thickening of the airway walls occur in a relatively early stage of the disease. Destruction of the airway walls causes chronic infection, and patients with ABPM finally suffer from chronic respiratory failure. When a specific antigen is *Aspergillus fumigatus*, ABPM is called "allergic bronchopulmonary aspergillosis". Instead of *Aspergillus fumigatus*, *Aspergillus niger* or *Aspergillus oryzae* can induce ABPM. Since *Aspergillus oryzae* is used for brewing miso and the soy sauce, ABPM is involved in occupational asthma. Other fungi such as *Penicillium, Cladosporium*, and *Candida* may be responsible for ABPM.

(2) Pathogenesis

Injured airway epithelial cells induced by asthma or cystic fibrosis lead to ABPM. It has been reported that HLA-DRB1 genes predispose to ABPM because Th2 reaction against *Aspergillus* easily occurs in patients with this genetic background.[113] After exposure to *Aspergillus*, it persistently infects the lower airway walls. After Th2 cells are activated, strong Th2 allergic reaction against *Aspergillus* occurs. Then, greater amounts of IgE and IgG antibodies against *Aspergillus* are produced through the production of IL-5 and granulocyte macrophage colony-stimulating factor (GM-CSF). *Aspergillus* secretes various types of proteases that cause tissue destruction and dysfunction of the airway epithelial cells. Then, not only eosinophilic but also neutrophilic inflammation is induced by IL-6 and IL-8 released from the airway epithelial cells and macrophages. Viscous sputum is retained in the central airways and mucoid impaction is formed. Subsequently, atelectasis and lung infiltration are formed.

(3) Diagnosis

Early diagnosis is important because any delay results in chronic airway infection and respiratory failure. The diagnostic criteria for ABPA include asthma, eosinophilia of the peripheral blood, positive results of immediate allergic reaction test against *Aspergillus*, positivity for precipitation antibodies against *Aspergillus*, elevated serum IgE levels, a history of lung infiltration, and central bronchiectasis. If all criteria are fulfilled, the diagnosis is considered as "confirmed"; if 6 of the 7 criteria are fulfilled, the diagnosis is considered as "almost confirmed".[114] However, early diagnosis or atypical case of ABPA does not match these criteria, and, recently, the criteria have been modi-

fied.[115] Greenberger *et al*. proposed new criteria for early diagnosis in patients with or without central bronchiectasis (ABPA-bronchiectasis and ABPA-seropositive, respectively). When ABPA is diagnosed, patients with positive skin test results or patients positive for specific IgE are thought to be susceptible to ABPA. Particularly, patients with high serum IgE levels, precipitation antibodies or specific antibodies against *Aspergillus* should be investigated. If the test results are positive, patients are diagnosed as ABPA-seropositive. Central bronchiectasis is diagnosed by chest computed tomography.

(4) Morbidity

About 2% to 3% of the patients with asthma are reported to be ABPA-seropositive in Japan. About half of them are diagnosed as ABPA-bronchiectasis.

(5) Treatment

Early diagnosis and treatment are important, and treatment should be started at the ABPA-seropositive stage. Environmental measures seem to be clinically effective for ABPA. In typical ABPA, lung infiltration reoccurs, and, consequently, the progression of central bronchiectasis and airway wall thickening are observed. During acute exacerbations, systemic steroids should be administered to improve lung infiltration and prevent irreversible airway destruction. In general, more than medium doses of steroid (predonisolone, 0.5 mg/kg) are administered. A steroid dose should be reduced over several weeks. During the chronic stage, ICSs are used along with long-term asthma treatment; however, in some cases, low doses of oral steroid are needed. To reduce the amount of *Aspergillus*, it is important to undertake environmental measures at home and at the office. For long-term management, the measuring of total serum IgE levels and chest radiography need to be routinely performed. A concomitant use of itraconazole is effective in the prevention of relapse, lung infiltration, reduction in serum IgE levels and sputum eosinophil count. The blood levels of itraconazole should be monitored because of the risk of side effects.

6.6.5. Heart failure

Symptoms of heart failure mimic those of asthma and a differential diagnosis is often difficult. The definition of acute heart failure is as follows: "Heart failure is caused by pump dysfunction induced by cardiac organic and/or functional disorder. Heart failure is also characterized by symptoms and signs induced by elevation of ventricular diastolic pressure and loss of perfusion in main vital organs." Heart failure is classified as acute decompensated heart failure, hypertensive acute heart failure, acute cardiac pulmonary edema, cardiac shock, high-output heart failure, and acute right ventricular failure. Symptoms of heart failure are dyspnea on exertion, palpitation and fatigue induced by the elevation of the left atrial pressure, and lung congestion at an early stage of left ventricular heart failure. In addition, patients with heart failure are characterized by anorexia, constipation, nausea, vomiting, feeling of fullness in the abdomen, leg edema, and body weight gain due to systemic congestion. In the later stages, torpor, oliguria, cyanosis, limb coldness, decline in memory function, disturbances of consciousness are observed as symptoms of congestive heart failure. In severe cases, episodic dyspnea at night and orthopnea develop. A prospective study of patients with heart failure showed the following symptoms during hospitalization: episodic dyspnea at night (55.4% of the patients), orthopnea (68.5%), coarse crackles (77.6%), gallop rhythm (40.5%), juggler venous distension (61.3%), leg edema (67.7%), and limb coldness (23.3%). If the above signs and symptoms are observed, there is a high probability of heart failure. In the case of heart failure, pulmonary vasodilation and heart enlargement are observed on a chest radiograph, in addition to other common signs such as Kerley lines, ground-glass opacity, butterfly pattern, or bat's wing pattern. When heart failure is suspected, the measurement of brain natriuretic peptide levels and serum N-terminal pro-B-type natriuretic peptide levels, echocardiogram, and Swan-Ganz catheter are useful tools that allow to diagnose heart failure and evaluate its possible causes and severity. Patients with heart failure may show obstructive lesions on spirometry as well as airway hyperresponsiveness. Systemic steroids and β_2-stimulant may worsen heart failure. Anticholinergic agents improve dyspnea and pulmonary function in patients with heart failure. Theophylline and aminophylline improve cardiac stress and pulmonary edema and are approved for use and covered by insurance in Japan. However, their blood levels should be carefully monitored because of low drug clearance. β-blockers are effective for the treatment of heart failure. Highly selective β_1-blockers are safe for asthmatic patients, and may be carefully administered to asthmatic patients with heart failure.

6.6.6. Gastroesophageal reflux disease

GERD is an esophageal disease characterized by heartburn. It is caused by the reflux of the gastric contents from the stomach into the esophagus, and induces various clinical symptoms and complications. GERD often causes chronic cough, throat pain, and noncardiogenic chest pain and sometimes induces asthma. Less than 5% of the Asian people are reported to have GERD, and the prevalence is lower than that in Western countries. About 6.6% to 37.6% of the Japanese people have GERD and the prevalence has been observed to increase recently. The prevalence of GERD in asthmatic patients is about 45% to 71% and is higher than that in the general population. Asthmatic patients with GERD have more asthmatic symptoms

than those without GERD and receive more oral steroids to relieve symptoms. A previous report showed that bronchoconstriction induced by asthma enhanced gastroesophageal reflux.[116] Moreover, other reports demonstrated that the clearance of gastric acid was reduced in patients with asthma, and a decrease of esophageal pH induced airway hyperresponsiveness and a decline in pulmonary function.[117] Proton-pump inhibitors are expected to improve the pulmonary function, QOL, and symptoms in asthmatic patients with GERD, while they are unable to improve asthma control or pulmonary function in uncontrolled asthmatic patients without GERD. If the symptoms are not improved by proton-pump inhibitors, a surgery for GERD is sometimes effective.

6.7. Occupational Asthma

Occupational asthma is defined as "asthma induced by exposure to a specific occupation-related substance in the office". Asthma control is often exacerbated by environmental factors found in the office. Recently, asthma exacerbated by work-related factors has been termed "work-related asthma". The incidence of occupational asthma in Japan is unknown, but about 9% to 15% of asthmatic patients in countries other than Japan have occupational asthma.

6.7.1. Causative substance

Various types of substances can cause asthma. They are classified into irritant substances (chlorine, acetic acid, smoke, and others) and sensitizing substances. Sensitizing substances are classified into high-molecular-weight substances, such as protein, and low-molecular-weight substances, such as chemicals. Occupational asthma is classified into sensitized and irritant-induced. Reactive airway dysfunction syndrome is classified as induced occupational asthma. Most of the high-molecular-weight substances and some of the low-molecular-weight substances (platinum salt, acid phthalic anhydride, and some others) induce sensitized occupational asthma. In this type of asthma, specific IgE against the causative substance is sometimes detected; therefore, it is expected that IgE may be involved in the development of asthma. Atopy and smoking are risk factors for sensitized occupational asthma.

6.7.2. Clinical presentation and diagnosis

A diagnosis of work-related asthma is mainly based on a medical history. It is necessary to evaluate whether patients are exposed to the causative substances in the office within 24 hours, whether asthma symptoms are improved during holidays or when out of office, or whether allergic rhinitis or allergic conjunctivitis is exaggerated in the office. It is difficult to diagnose sensitized occupational asthma only by medical interview. Therefore, it is also necessary to monitor PEF 4 times a day (at least for 2 weeks in the office and 2 weeks out of office). It is also useful to evaluate airway hyperresponsiveness and measure sputum eosinophil count in or out of office and to perform a skin prick test or detect specific IgE. A challenge test is also a useful diagnostic tool. Detection of specific IgE may be useful but the availability of commercially available detection kits or drugs is limited. To diagnose irritant-induced occupational asthma, medical interview is the most important when it reveals that asthma symptoms are induced within 24 hours after exposure to an occupation-related irritant.

6.7.3. Treatment

Treatment in occupational asthma involves various measures to ensure reduction of the causative substances in the office. Continuous exposure aggravates symptoms and worsens pulmonary function. Avoidance of exposure is insufficient to improve symptoms. In occupational asthma induced by latex, the use of nonlatex gloves is recommended. Pharmacological treatment is generally similar to the treatment of asthma. ICSs are effective in sensitized occupational asthma in addition to the avoidance of exposure to causative substances. After a causative antigen has been identified, if patients are unable to avoid exposure, allergen immunotherapy may be effective. A recent report has shown that monoclonal anti-IgE antibody was effective in a patient with severe occupational asthma who worked at a bakery.[118] If patients are unable to avoid exposure to causative substances, the change of the occupation or workplace may be inevitable.

6.7.4. Precautions

As primary precaution, environmental measures including clearance or reduction of the causative substances at the office are important. Improvements in work methods and in ventilation and cleaning of the office are necessary. If needed, workers should wear a mask and use protective equipment. As secondary precaution, medical surveillance is required to avoid exacerbations when sensitized occupational asthma occurs at the office. Patient questionnaires, spirometry, measurement of serum specific IgE levels, and skin prick test should be repeated regularly.

6.8. Surgery

Although numerous studies have shown that patients with asthma often experience respiratory complications such as bronchoconstriction or barotrauma during the perioperative period, a previous report showed that only 1.7% of asthmatic patients who underwent a surgery had bronchoconstriction during the perioperative period.[119] In addition, respiratory complications do not cause pneumothorax, pneumonia, or death. The incidence of respiratory complications is associated with the severity of asthma, type of surgery (surgeries of the chest and upper abdomen

carry a higher risk), or the method of anesthesia (intubation and sympathetic nerve block carry a higher risk). Before surgery, the severity of asthma should be evaluated on the basis of clinical history, symptoms, physical examination, and pulmonary function, and the method of anesthesia should be determined. To additionally treat asthma, the condition of patients should be evaluated at least several days prior to surgery.

6.8.1. Management before surgery

(1) Evaluation of the severity of asthma

The severity and control of asthma should be accurately evaluated in terms of the clinical history, symptoms, physical examination, pulmonary function, PEF values, and arterial blood gas analysis. A physician needs to assess the current treatment, use of asthma medications, history of surgeries, and allergy to latex. A history of allergy to NASIDs after the onset of asthma should be confirmed because it affects the choice of analgesic agents.

(2) Timing of surgery

Surgery should be performed during the stable period of asthma without exacerbations. If asthma is poorly controlled and the surgery can be postponed, additional treatment should be administered until good control and normal pulmonary function are achieved. If an emergency operation is required in unstable patients, asthma should be controlled with systemic steroid during the perioperative period.

(3) Pharmacological treatment

If the current treatment is sufficient to maintain good control of asthma, it should be continued. If the condition is unstable, additional treatment should be considered. ICSs should be given if the patient is steroid-naïve without any symptoms, and there is enough time to administer an ICS. If the condition is unstable, FEV_1 is less than 80%, or PEF values against personal best values, treatment with oral corticosteroids (predonisolone, 0.5 mg/kg/day, for 3-7 days) should be considered. If there is not much time left before the surgery or oral steroids cannot be administered, an intravenous administration of corticosteroids should be considered. There is no evidence as to the duration of treatment and required steroid doses. If patients continue to take oral steroids for more than 6 months, steroid cover should be considered during the perioperative period. Although hydrocortisone at a dose of 100 mg/day is generally administered day before the surgery, and 100 mg every 8 hours on the day of surgery, the doses and intervals in treatment should be reviewed in the future. If the patient takes a high dose of ICSs and will not be able to inhale the drug during the perioperative period, an intravenous administration of a systemic steroid should be considered. As soon as the patient is able to inhale the drug again, a systemic steroid should be switched to an ICS.

6.8.2. Anesthesia

(1) Local and spinal anesthesia

Local or spinal anesthesia is performed in small surgery or peripheral injury without any effect on the respiratory system. Sympathetic nerve blockade by high spinal and epidural anesthesia may induce bronchoconstriction and asthma attack. In patients with a history of allergy to local anesthetic agents, a skin prick test or intradermal challenge test should be performed. Diphenhydramine is reportedly used instead of local anesthetic agents.

(2) General anesthesia

Although general anesthesia can be safely performed in proper respiratory-care setting, intubation may induce bronchoconstriction in asthmatic patients. Anesthetic agents with bronchodilatory action are used to induce and maintain anesthesia. Intubation should be performed after sufficient anesthetic depth has been achieved. Humidification of the inhaled air, prevention of dehydration, and intravenous lidocaine injection prior to intubation should be considered.

(3) Anesthetic agents

Of inhaled anesthetics, dinitrogen monoxide, isoflurane, and sevoflurane are generally used. Among them, sevoflurane is the first-choice drug for asthmatic patients. Aminophylline and β_2-stimulants may induce ventricular arrhythmia under anesthesia with halothane; therefore, isoflurane or sevoflurane should be used. Of intravenous anesthetics, thiopental, thiamylal, ketamine, propofol, midazolam, remifentanil, and fentanyl are used. The use of thiopental and thiamylal is contraindicated in asthmatic patients owing to bronchoconstrictive action of these drugs. Although propofol has bronchodilatory action and is used in inducing anesthesia, it should be administered with caution because of possible bronchial spasm.

6.8.3. Treatment of asthma attack during surgery

When asthma attack occurs during surgery, inhaled β_2-stimulant, intravenous drip infusion of corticosteroid (hydrocortisone, methylprednisolone) and aminophylline, subcutaneous injection of adrenaline (0.1%), and inhalation of oxygen are recommended.

6.8.4. Postoperative management

After awakening, the patient should be extubated. Because asthma attack is often induced by various stimuli after the surgery, it is important to monitor the patient carefully. When wheezing continues after the surgery, β_2-stimulant is inhaled before extubation and sufficient dose of a systemic steroid should be administered. If AIA cannot be excluded, NSAIDs must not

be used. Morphine hydrochloride is contraindicated because it may induce bronchoconstriction.

6.9. Cough-Variant Asthma

Cough-variant asthma (CVA) is characterized only by chronic dry cough without wheezing, attack of dyspnea, and abnormal pulmonary function. If cough continues for more than 8 weeks, it is called chronic cough. CVA is the major cause of chronic cough. In Japan, chronic cough is caused by CVA (36% of the cases), atopic cough (16%-29%), sinobronchial syndrome (16%-17%), postinfectious cough (2%), and GERD (2%).[120] Cough variant asthma is distinguished from asthma by the lack of wheezing. CVA belongs to the subgroup of asthma or intermediate asthma and is similar to asthma in the following aspects: (i) airway hyperresponsiveness is mild (intermediate between patients with mild asthma and healthy individuals)[121]; (ii) cough sensitivity is within the normal range; (iii) atopic state is common; (iv) eosinophils are noted in sputum or induced sputum; (v) eosinophilic infiltration is noted in the bronchial mucosa; (vi) eosinophils are increased in the bronchoalveolar lavage fluid; (vii) fraction of exhaled nitric oxide (FeNO) is increased; and (viii) inhaled or oral corticosteroids are effective. Bronchodilators, including β_2-agonists, are effective for cough. CVA is not usually accompanied by sputum, is more severe at bedtime, during the night and early morning, and is induced by cold and warm air, passive smoking, conversation, exercise, alcohol, mental stress, and others. About 30% of the patients with CVA develop wheezing asthma. Since cough can be prevented with an ICS, long-term management with an ICS is recommended.

Atopic cough is similar to "non-asthmatic eosinophilic bronchitis" in Europe and the United States.[122] Atopic cough is somewhat similar to CVA in clinical symptoms, and has the following features: (i) presence of the atopic state; (ii) bronchodilators such as β_2-agonists are ineffective; (iii) there is no airway hyperresponsiveness; (iv) cough sensitivity is increased; (v) H_1-antagonists and steroids are effective; and (vi) asthma does not develop. Long-term management is unnecessary. In addition, unlike in CVA, FeNO levels do not increase. Other important diseases, differentiated from chronic nonproductive cough, include cough caused by postnasal drip, gastroesophageal reflux, or angiotensin-converting enzyme inhibitors.

6.10. Aspects of Psychosomatic Medicine

Psychosomatic factors have long been reported to be associated with asthma. As early as in the years 400 to 300 BC, Hippocrates postulated that feeling of anger or animosity could be involved in asthma attack. Many reports have demonstrated that asthma control is strongly affected by psychosomatic factors. It has been reported that psychosomatic and social background as well as family lifestyle affect the development, exacerbations, and management of asthma.

6.10.1. Psychosomatic background

(1) Stress and asthma

Asthma control is affected by stress. Particularly, depression or panic disorder is observed in patients with mild asthma who are treated by general physicians. Associations between depressive tendencies and hospitalization rates and between panic disorder and emergency room visits have been reported.[123] To reduce healthcare cost and severity of asthma, early diagnosis and treatment of depression, panic disorder, and other stress-related conditions are needed.

(2) Current adherence rates

Adherence to treatment is important in asthma control. According to a previous study in pediatric patients, although the mean rate of ICS use recorded by patients in their asthma diaries was 94.5%, the actual mean rate was 58.4% as measured by the electronic counter in inhaler devices. Similar results have been reported for adult asthma.

(3) Consequences of severe asthma or death from asthma

Patients who had a near-fatal attack are characterized by large fluctuations in PEF values, poor adherence to treatment, and poor asthma control compared with patients who did not have a near-fatal attack. Moreover, it has been reported that these patients have limited capacity to adapt to treatment and psychosomatic disorders that negatively affect asthma management.

6.10.2. Diagnosis of asthma in psychosomatic medicine

(1) Development, relapse, exacerbation, and persistence of asthma due to psychosomatic stress

When psychosomatic stress is an exacerbating or triggering factor, changes in lifestyle and various events (childbirth, marriage, divorce, moving house, losing a job, job change, hospital admission, death of a close relative) or stresses of daily life (at home, work, school, etc.) are often observed prior to the development or relapse of asthma. There is a close relationship between the psychological condition (anxiety, tension, anger, depression, etc.) and asthma symptoms.

(2) Social adaptation problems associated with asthma

Asthma is a chronic disease with frequent exacerbations and relapses during its clinical history. The disease is associated with considerable physiological, psychological, temporal, and economic burden. Asthma sometimes induces psychological distress and negatively affects social and professional life of

the patients, often resulting in the development of psychosomatic disease. This, in turn, is associated with sleep disorders, problems in personal relations, social isolation, worse performance at school or work, depression, and anxiety.

(3) Nonadherence to asthma treatment

Psychosomatic factors may lead to poor adherence to asthma treatment. Consequently, they adversely affect the course and outcomes of treatment. Moreover, they cause irrational anxiety, fear, and the sense of helplessness in controlling the disease, as a result of which, patients often develop distrust in physicians or medical care. This leads to treatment failure or considerable delays as well as inadequate self-management. Patients with maladaptation to stress tend to have more severe and refractory asthma. Sometimes, it is impossible to stop systemic steroid treatment in these patients, which can even lead to death. Symptoms of asthma are closely related with recognition of patients' own treatment and management, so questionnaires such as the Perceived Control Asthma Questionnaire have been developed for evaluating the state of recognition of medication.

6.10.3. Psychophysiological treatment

Counseling is the principal method in psychophysiological treatment. Providing acceptance, sympathy, and support to patients helps them express emotions, recognize the relationship between the mind and body, and manifest emotional problems. In addition, pharmacotherapy, autogenic training, cognitive behavioral therapy, family therapy, and fasting therapy are attempted. Diary writing alone has been reported to improve the symptoms of asthma in psychosomatic patients.[124] If asthmatic patients with anxiety disorder or mood disorders often suffer from exacerbated asthma, antianxiety or antidepressant agents may be effective in the management of an asthma attack in addition to regular asthma drugs. If the actual stress is more causative than some aspects of the patient's personality, autogenic training is useful. For personality issues, a physician should consult a specialist in psychosomatic medicine, or a team approach with psychotherapist and specialist is recommended.

6.11. Immunization

6.11.1. Guidelines on immunization

(1) Perspective of the Japanese Society of Pediatric Allergy and Clinical Immunology

The guidelines on immunization were revised in 2012; they present the perspective of the Japanese Society of Pediatric Allergy and Clinical Immunology.

(2) Constituents of vaccine relating to allergy

Constituents of vaccine that are related to allergy include egg-related antigen, antiseptic agents or additive substances, medium or antimicrobial agents, and vaccine antigens. Latex allergy may sometimes be problematic (yellow fever vaccine).

6.11.2. Precautions in immunization in asthmatic patients

In the USA, immunization is recommended for asthmatic patients except for specific cases since asthmatic patients tend to exaggerate serious symptoms and attack with respiratory infection. In general, immunization of live viral vaccine can be used in asthmatic patients with low-to-intermediate doses of systemic steroids (lower than 20 mg/day). However, live viral vaccine should be discontinued a month later in patients receiving 2 mg/kg/day or more than 20 mg/day of prednisolone over 2 weeks.

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